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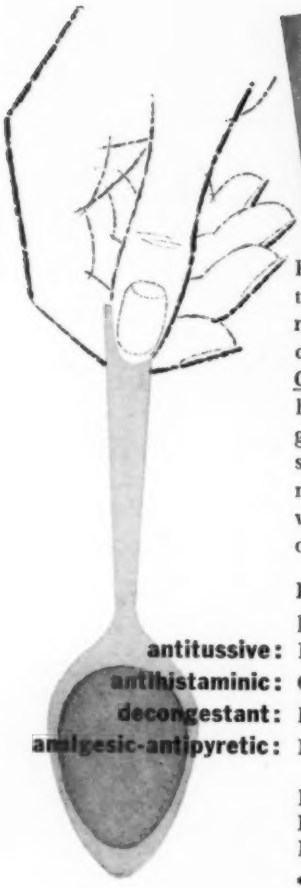

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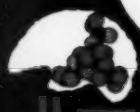

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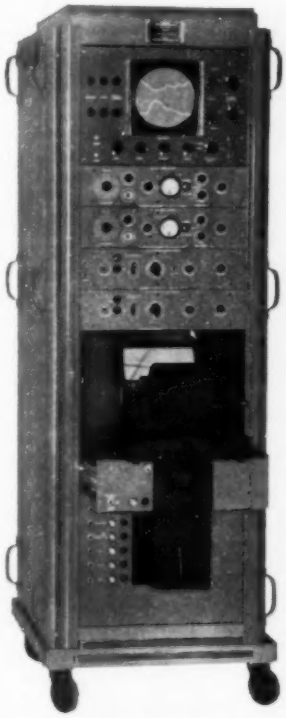

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1. McHardy, G. and Browne, D.: South. M. J. 45:1139, 1952. 2. Hufford, A. R.: Rev. Gastroenterol. 18:588, 1951. 3. Johnston, R. L.: J. Indiana M. A. 46:869, 1953. 4. Miller, B. N.: J. South Carolina M. A. 48:245, 1952.

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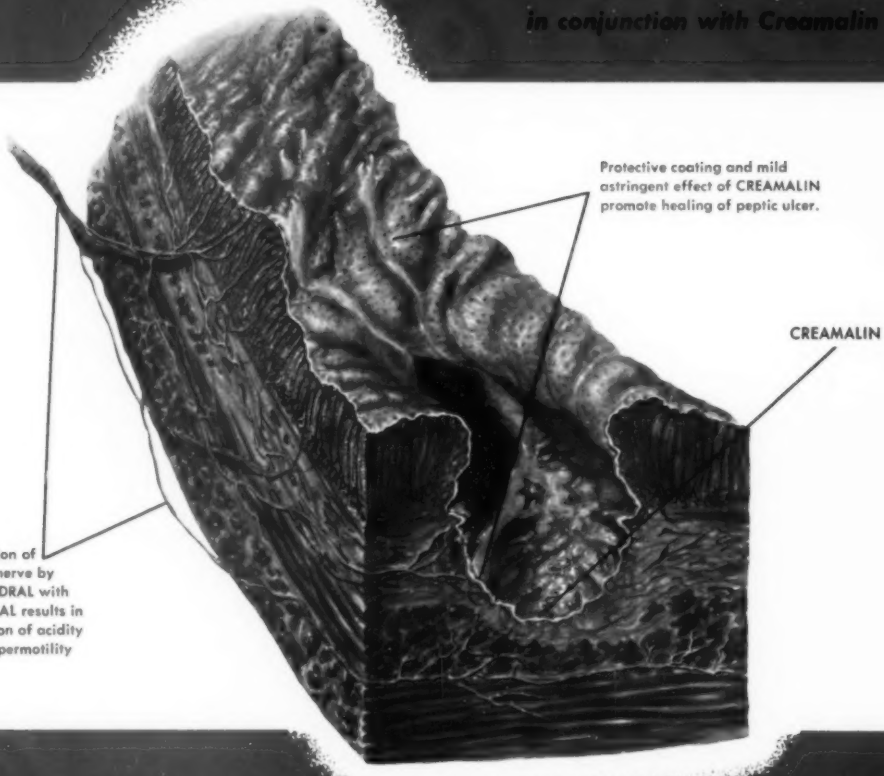
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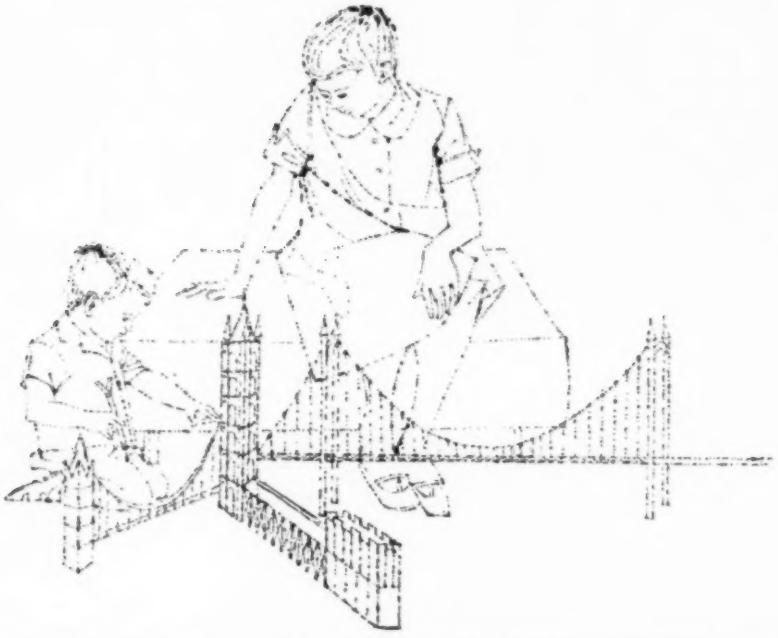

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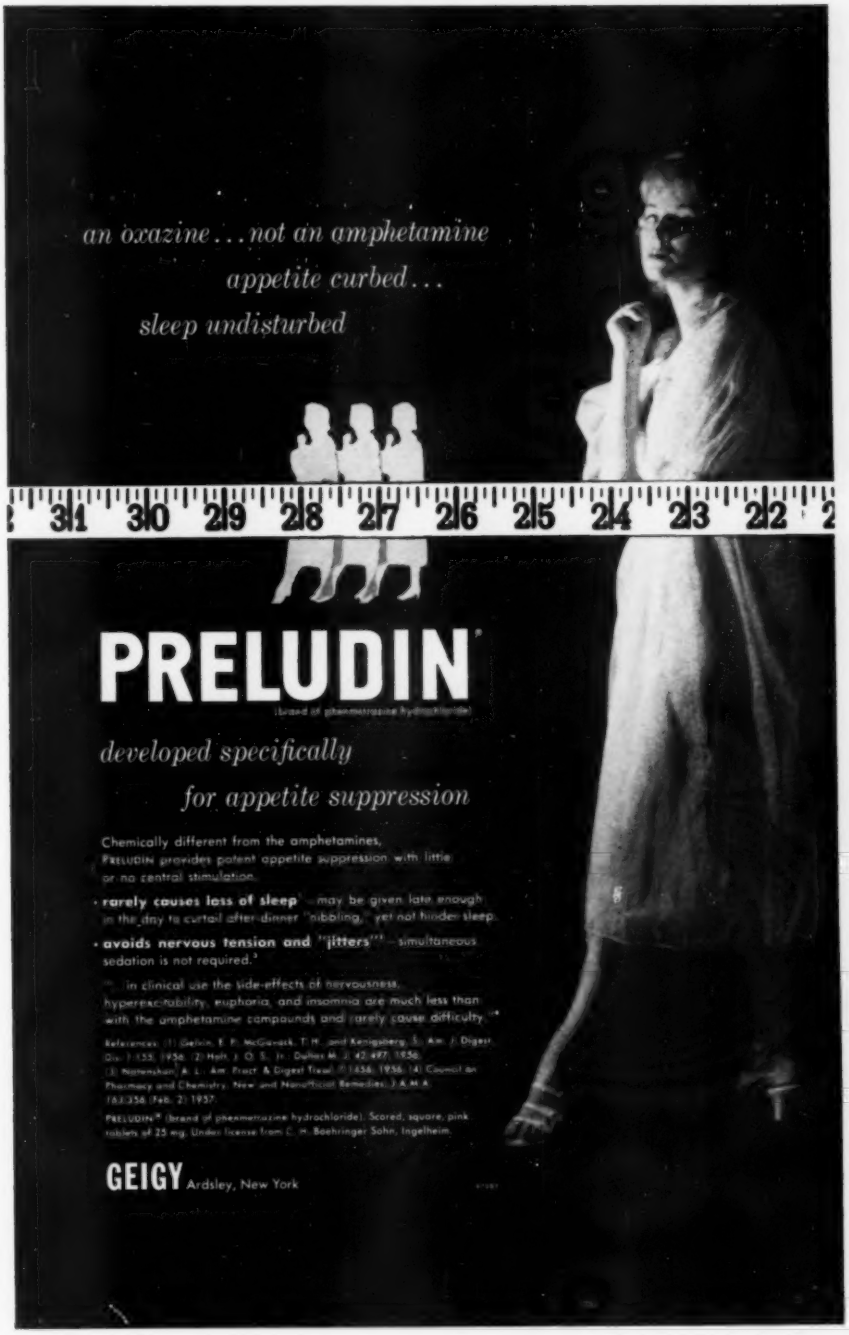
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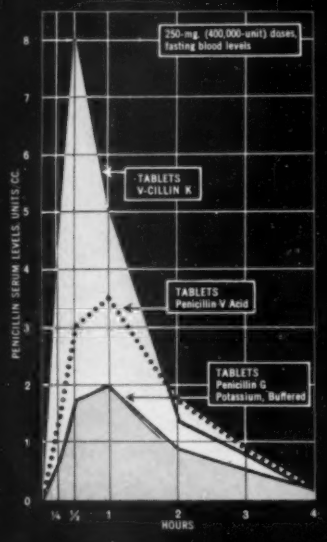

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 33, NO. 11 NOVEMBER 1957

THE NINTH A. WALTER SUITER LECTURE

A Symposium on Obesity

Under the Auspices of the Committee on Public Health of
The New York Academy of Medicine

Presented at the Stated Meeting of the Academy, December 6, 1956

CORRELATION BETWEEN METABOLISM AND FEEDING BEHAVIOR AND MULTIPLE ETIOLOGY OF OBESITY

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NEURAL FACTORS IN OBESITY

JOHN R. BROBECK

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University of Pennsylvania, Philadelphia, Pa.

PSYCHOLOGICAL ASPECTS OF OBESITY

WALTER W. HAMBURGER

Associate Professor of Psychiatry, University of Rochester School of Medicine and Dentistry,
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CORRELATION BETWEEN METABOLISM AND FEEDING BEHAVIOR AND MULTIPLE ETIOLOGY OF OBESITY*

JEAN MAYER, Ph.D., D.Sc.

Associate Professor of Nutrition, Harvard University Department of Nutrition, Harvard School of Public Health, Boston, Mass.

INTRODUCTION

THE choice of "Obesity" as the subject of a symposium to honor the memory of A. Walter Suiter is topical. Few abnormalities are the object of such widespread interest both among the medical profession and among the public. The fact that this symposium is held under the auspices of the Committee on Public Health of the Academy is also appropriate. There is little doubt that the prevalence of obesity in this country is on the increase, and that it is accompanied by increased mortality from a number of degenerative diseases.[1] There is of course a strong possibility that, in many cases, the relationship between the disease and obesity is association rather than causation; some, such as the relationship between obesity and diabetes, may be even more complex and involve both association and causation.[2] There is also a likelihood that body type and the distribution of weight may provide a better correlation with incidence of associated diseases than "excess weight" as such.[3] Still, all in all, the relationship with disease is close enough to allow obesity to be considered a serious public health problem, even though this lecturer believes, with Keys,[4] that it is not the "Number One" Public Health problem in this country at the present time as some would have us believe.

In this lecture, I shall attempt to emphasize some of the metabolic aspects of the regulation of food intake; I shall illustrate the many possibilities of error in the regulation leading to obesity: both from the etiological point of view of the nature of the primary disturbance

* Presented at the Stated Meeting of The New York Academy of Medicine as part of the Ninth A. Walter Suiter Lecture, a *Symposium on Obesity*, December 6, 1956.

The part of the work presented in this lecture which was executed in this lecturer's laboratory, was supported in particular by grants from the National Institute of Arthritis and Metabolic Diseases (Grant No. A-49) Bethesda, Md., and the Nutrition Foundation, Inc., New York.

causing obesity and from the point of view of pathogenesis, i.e., the mechanism of the development of obesity. I shall suggest some practical applications to therapy. I rely of course on my distinguished fellow-speakers to cover, respectively, purely neurological aspects (Dr. J. R. Brobeck[5]) and the psychiatric aspects (Dr. W. W. Hamburger[6]). Finally, I should indicate that those of my listeners who are interested in more thorough bibliographical references will find them in two extensive reviews published in 1953[7] and 1955.[8]

Interaction of Hypothalamic Centers and Metabolism: The "Glucostatic" Component in the Regulation of Food Intake

Localization of hypothalamic structures concerned with food intake and some of their characteristics are excellently reviewed by Dr. John Brobeck[5] elsewhere in this symposium. However, it might be of interest to indicate how behavioral techniques may clarify the physiological function of such centers. Using a modification of the Skinner technique of "operant conditioning"*[9] it was possible to follow and record for several days and even weeks the feeding behavior of animals, e.g., mice, with the ventromedial hypothalamic area damaged by stereotaxic lesions[10] or by goldthioglucose.[11] Under the conditions of the experiment, normal animals exhibit during the course of a day a period of fast rate of eating followed by a period of satiety. Animals with ventromedial hypothalamic lesions do not show any increase of the rate of ingestion (which constitutes a behavioral measure of hunger) over the maximal rate of normal animals. But the "satiety" plateau has disappeared. This finding appears to confirm that, as suggested by Anand and Brobeck,[12] the role of the ventromedial area is to brake a constantly activated feeding area. It was also shown that lesions of the ventromedial area due to goldthioglucose administration eliminate the increase in food intake which, in normal animals follows chronic exposure to cold[13] and to exercise.[14] It thus seems probable that the way in which the metabolic state intervenes to regulate food intake is through inhibitory influences mediated by the ventromedial area rather than through facilitating influences mediated through the feeding area.

The exact function of this feeding area is not yet altogether clear.

* The animals are trained to press on a lever to obtain a reward which is delivered according to pre-set schedules. In the adaptation to problems of food intake, the delivery of each small pellet of food corresponding to a mouthful is recorded.

In an important study Anand and Brobeck[12] showed that electrolytic lesions in the lateral hypothalamus caused aphagia. No special consideration was given to water intake. We observed[15] that when large lesions were made in the same area, the animals, besides being aphagic, were also completely adipsic.* Daily loss of body weight in these animals was greater than that of rats subjected to pure starvation but the weight loss pattern was closely simulated by normal rats given access to food but completely deprived of water. Some rats showed spontaneous recovery of eating three to eight days postoperatively. The occurrence of such recoveries has been noted by Teitelbaum and Stellar.[16] However, in recovering animals, reappearance of water intake slightly preceded recovery of food intake. It thus appears that at the present, definite interpretation of the lateral area as a "feeding" area as such must await proof that the aphagia is not secondary to adipsia.

The nature of the mediating mechanism between metabolic influences and hypothalamic inhibitory impulses is of obvious interest. A theory proposed by Strominger and Brobeck,[17, 18] which saw heat phenomena, in particular those associated with specific dynamic action of food, *directly* regulating food intake, has been reviewed critically elsewhere.[7] While it appears doubtful that such phenomena do in fact play a direct role in the quantitative adjustment of intake to requirements, a degree of facilitation or inhibition attributable to small temperature variations in the hypothalamus remains an interesting possibility. Similarly, the limited but intriguing theory of Soulairac[19] which puts primary emphasis on carbohydrate absorption through the gastrointestinal tract has been reviewed previously.[7] While it has been confirmed that prolonged over-consumption of a high carbohydrate diet increases rates of intestinal absorption of glucose,[20] this phenomenon has been shown to be probably secondary to hyperphagia; while it may act to perpetuate dysfunctions, it is unlikely to have etiologic significance. It serves however to remind us that there is a gastrointestinal component in the hunger-satiety complex.

The "glucostatic" hypothesis, proposed by the author and his associates[7, 8] postulated that the influence of the metabolic state on feeding behavior and its role in regulating food intake were mediated through the rate of passage of glucose (or of ions associated with the passage

* The lesions, extended from just rostral to the posterior hypothalamic nucleus to just caudal to the supraoptic nucleus and from just ventral to the fornix to the base of the brain. Their centers were lateral to the fornix and the lesions touched the inner boundary of the pyramids. The supraoptic nuclei, ventromedial hypothalamic nuclei and the fornix were undamaged.

of glucose, e.g., potassium and glucose phosphate) into the cells of the ventromedial hypothalamic area. The theory appeared difficult to test directly because of the apparent inaccessibility of this well protected hypothalamic area. For this reason, efforts were concentrated at first on correlation of behavioral states with peripheral measurements of glucose utilizations which could be considered as generally representative of utilization by the critical midbrain area. In particular, it was shown[21] that in man, the presence or absence of hunger sensations in normal individuals subjected to various nutrition states and in diabetic patients correlated well with, respectively, large and small arteriovenous or capillary venous glucose differences ("Δ glucose"); these, of course, are indicators of availability of carbohydrates to extrahepatic tissues.

Stunkard and Wolff[22] confirmed these findings and in addition showed that the presence of gastric "hunger" contractions correlated well with subjective hunger feelings and small Δ-glucose values, while the absence of hunger contractions correlated well with absence of hunger feelings and large Δ-glucose values.

The fact that glucose infusions do not invariably eliminate hunger had been construed by Bernstein and Grossman[23] to be an insuperable objection to the glucostatic theory. The question was successfully re-examined by Stunkard and Wolff[24] who infused glucose in 40 normal and diabetic subjects. They administered 50 ml. of a 50 per cent solution. Gastric "hunger" contractions were eliminated in 19 subjects. Ten and twenty minutes after the infusion arteriovenous differences were significantly higher in the subjects in whom gastric contractions were eliminated, indicating a more active utilization of carbohydrates in these individuals. In 14 of the 19 subjects in whom the contractions had been stopped, contractions resumed, after a lapse lasting on the average 47 minutes. In the five other subjects A-V differences ("Δ-glucose") remained elevated.

A more reproducible method of increasing the availability of carbohydrates to non-hepatic tissues is through the administration of glucagon, the pancreatic glycogenolytic factor which acts apparently through activation of hepatic phosphorylase. Glucose thus released is well utilized and both blood glucose level and Δ-glucose are invariably increased when this hormone is administered. Over 50 experiments on human subjects have been conducted since the appearance of the first note on the effect of glucagon on gastric hunger contractions.[25] In all

cases, gastric contractions and hunger sensations are immediately and strikingly eliminated by glucagon administration. At the same time, Δ-glucose values are drastically increased. As these, after a variable interval, wane, hunger sensations and gastric contractions reappear even at absolute levels of blood glucose which are still higher than the fasting values. Particularly striking is the observation of Stunkard[26] on a decorticate starved patient in whom continuous gastric hunger contractions were eliminated by glucagon administration while attempts by other methods (excluding food) had failed. The observations in human subjects on elimination of gastric contractions by glucagon have been reproduced in rats where the use of intragastric balloons has been introduced. In these animals it is possible to correlate the presence or absence of gastric contractions with behavior through the use of operant conditioning techniques.[27]

An even more cogent indication in favor of a glucostatic component in the regulation of food intake is that goldthioglucose, but not other goldthio-compounds of similar toxicity, produces destructive lesions in the ventromedial hypothalamic area.[12, 28] These lesions are most severe in the ventromedial nuclei but also involve the ventral part of the lateral hypothalamic area, the arcuate nucleus and the median eminence. Goldthiosorbitol does not cause such lesions nor does it produce obesity, in spite of the structural similarity between glucose and sorbitol. Similarly, compounds in which gold is linked by a sulfur bridge to normal metabolites other than glucose, such as malic acid, caproic acid or glycerol, do not induce hypothalamic lesions or obesity. Goldthioglucose hypothalamic lesions can be induced in the rat as well as in the mouse.[28] It thus appears that gold is dragged into the ventromedial hypothalamic cells which it destroys because of the peculiar affinity for glucose displayed by these cells. This particular hypothalamic area had already been shown by Forssberg and Larsson[29] to exhibit a typical glucose and phosphate metabolism. Incidentally, it is worthy of note that hypothalamic lesions induced by goldthioglucose are much more "purely" hyperphagic than lesions performed in the same area by electrocoagulation. Goldthioglucose obese animals do not display to the same degree the associated symptoms, such as gonadal dysfunction or disturbance in water balance, seen in animals made obese through hypothalamic lesions obtained by electrocoagulation. The histologic figures of goldthioglucose lesions also confirm that functional localiza-

tion is not limited to a given nucleus but that greater or lesser densities of glucoreceptive cells with food intake regulating functions are to be found throughout the ventromedial hypothalamus, interspersed with cells performing other functions.

Thus we arrive at the following conception: There are, as Drs. Brobeck[5] and Hamburger[6] expound elsewhere in this symposium, a great many physiologic and psychologic factors influencing food intake; these may intervene at several levels in the central nervous system, in particular the lateral hypothalamic area, the thalamus, the frontal lobes and other parts of the brain cortex. Among these factors, the metabolic state of the organism is of particular importance; it is the factor which "regulates" food intake, i.e., which adjusts intake to output.*

At least part of the mode of action of this factor is through a glucostatic mechanism based on the ventromedial hypothalamic area. While a part of the awareness of *hunger* is through awareness of gastric contractions, (which in turn may be controlled in part by central deprivation), it appears that it is not through activation of hunger as such but through the application of a *satiety* brake that this ventromedial glucostatic mechanism operates.

The quantitative operation of the regulating mechanism is still mysterious. Some indication of the over-all characteristics are of course available. In the adult animals, Cowgill[32] and Gasnier and A. Mayer[30] have shown that the intake is in constant ratio to the output. A. Mayer further showed that in caged animals the precision of regulation was better when the energy output was increased by exposure to cold. Our results have shown that similarly, the precision of the regulation is better when animals and men have to perform moderate exercise than when they are inactive.[8] In growing animals, food intake seems to be so determined that the thermochemical efficiency of growth, i.e., the ratio of calories deposited to calories ingested is constant from weaning to puberty.[33] On poorer diets, the thermochemical efficiency of growth declines somewhat earlier. It also appears that besides the short term mechanism—probably glucostatic—operating to adjust intake to output, another slower and somewhat sluggish mechanism intervenes which corrects on a long-term basis imprecisions of the short-term mechanism and permits greater constancy of adult size and growth rate.

* The characteristics of the mode of regulation, limits, precision, reproducibility, etc. first elaborated by Gasnier and A. Mayer[30] have been reviewed in a recent report.[31]

TABLE I.—TYPES OF OBESITY*

In mice	
Genetic:	"Yellow" obesity, associated with coat color; heterozygous, dominant character; normal mating. "Hereditary obese hyperglycemic syndrome"; homozygous, recessive character associated with absence of mating. "NZO" obesity; homozygous recessive character, normal mating.[34]
Of hypothalamic origin:	Spontaneous Surgically induced Induced by goldthioglucose.[11]
Of endocrine origin:	Caused by injection of pituitary tumors secreting adrenocorticotrophic hormone.
Otherwise induced:	By high-fat diet.
In rats	
Genetic:	Associated with diabetes.
Of hypothalamic origin:	Induced by bilateral or unilateral lesions.
Of other central nervous system origin:	From frontal lobe damage.
Of endocrine origin:	From hypertrophy of adrenal cortical tissue. From prolonged treatment with protamine zinc insulin, or insulin with forced feeding. After thyroidectomy with hypothalamic lesions or with forced feeding.
Otherwise induced:	By immobilization. By high-fat diet, Osborn-Mendel Strain.[35] By conditioning.[36]
In dogs	
Genetic:	In the Shetland sheepdog, recessive character.
Of hypothalamic origin:	Spontaneous. Surgically induced. Due to paraventricular degeneration caused by corticotrophin or cortisone.
Otherwise induced:	By immobilization.
In monkeys	
Of hypothalamic origin:	Surgically induced.
Of other central nervous system origin:	Surgically induced by lesions of the thalamus.
In farm animals	
Genetic:	In strains selectively bred for fat, in particular, pigs bred for lard.
Of endocrine origin:	Induced by castration and by estrogens in the fowl; by castration and implants of estrogens in male cattle.
Otherwise induced:	By immobilization in pigs, cattle and geese; by forced feeding in geese for production of foie gras.

[*Table 1 continued on next page*]

In man

Genetic:	A multiplicity of genes have been studied by Newman, von Vershuer, Bauer, Gurney, Rony, Angel and others, reviewed by Mayer. In congenital adipose macrosomia. In monstrous infantile obesity. Associated with Laurence Moon Biedl syndrome. Associated with hyperostosis frontalis interna. Associated with von Gierke's disease. In familial hypoglycemosis (congenital lack of alpha cells).
Of hypothalamic origin:	In dystrophia adiposogenitalis, with discrete or diffuse hypothalamic injury; occasionally with panhypopituitarism and narcolepsy; Kleine Levin syndrome.
Of other central nervous system origin:	After frontal lobotomy. In association with cortical lesions, in particular, bilateral frontal lesions.
Of endocrine origin:	With insulin-producing adenoma of the islets of Langerhans, with diffuse hyperplasia of the islets, and in association with diabetes. With chromophobe adenoma of the pituitary without hypothalamic injury. In Cushing's syndrome (hyperglycocorticoidism). From treatment with cortisone or adrenocorticotrophic hormone. In the Bongiovanni Eisenmenger syndrome. In disorders of the reproductive system: gynandrism and gynism, aspermatogenic gynecomastia without aleydigism; male hypogonadism (sometimes with bulimia), postpuberal castration, menopause, ovarian disorder, paradoxical Gilbert Dreyfus disorder. In pseudohypoparathyroidism.
Otherwise induced:	By immobilization in adults and children. By psychic disturbance. By social and cultural pressure.

[a] The only references included in this table are those not included in the original table because of later discovery or identification.

It is possible that the operation of this slow long-term mechanism rests on the state of the fat depots at a given time.[8, 31]

Multiple Etiology and Dual Pathogenesis of Obesity

The development of the various forms of obesity can be considered either from the point of view of etiology or from the point of pathogenesis. The point of view of etiology has been developed at length in a previous review,[7] in which genetic, traumatic and environmental factors were distinguished. Obviously, such a distinction, although

useful, entails a certain degree of oversimplification; for obesity to develop, there has to be permissive interaction of genetic and of environmental factors, or genetic, traumatic and environmental factors. However, this very simplification permits a useful classification, through the singling out of the characteristic element in the etiology. Table I is an adaptation of a table given in a recent and more extensive review,[8] which gives references for the different types cited.

The author and his associates[8] have also been led to introduce a general distinction between "regulatory" obesities, where the primary impairment is one of the central mechanism regulating food intake, and "metabolic" obesities, where the primary lesion is an inborn or acquired error in the metabolism of tissues other than the regulating centers. In the first case, habitual hyperphagia may lead to secondary metabolic abnormalities. In the second case, peripheral metabolic dysfunction may in turn interfere with the proper function of the central nervous system. This difference has been illustrated in our laboratory by comparisons between different types of obesity in mice.

"Regulatory" obesities are illustrated by the hypothalamic obesities induced either by surgical (stereotaxic) bilateral destructions of the ventromedial nuclei[10] or by extensive symmetrical destructions in the ventromedial area after goldthioglucose administration.[11] Mice with these syndromes show hyperphagia and their weights may reach four times the normal. Their rate of lipogenesis and cholesterogenesis (as measured by incorporation of radioacetate into hepatic and extrahepatic fatty acids and cholesterol, *in vivo* and *in vitro*) is increased in the measure that they are allowed to overeat. Fasting brings lipogenesis down to normal fasted levels.[37-39] The rate of glucose absorption by the intestine is increased, but again this appears to be a non-specific consequence of hyperphagia.[20] Blood cholesterol and glucose levels may be slightly elevated in elderly very obese animals but this appears to be a direct result of their "lipoplethoric" state.[2, 8, 40] When such obese animals are reduced by fasting, their body composition returns to normal as their weight returns to normal.[8]

The situation in "metabolic" obesities such as the hereditary obese hyperglycemic syndrome[7, 8] or the obesity due to the grafting of ACTH secreting pituitary tumors[41-43] is in striking contrast.

Obese hyperglycemic mice show an obesity as extreme as that seen in the hypothalamic types. Though their hyperphagia is usually less

pronounced, they derive their caloric surplus in part from the relative inactivity. They are either markedly hyperglycemic or hyperglycemia can be readily elicited by administration of growth hormone, to which the blood glucose of normal littermates (or of littermates made obese by hypothalamic lesions-stereotaxic or goldthioglucose) shows little or no reaction. They show marked hypercholesterolemia. They display a variety of atypical responses to the effect of hormones. While means of "physical" defense against cold (such as piloerection, vasoconstriction, etc.) are intact, obese hyperglycemic mice are incapable of raising their metabolism in the cold and as a result die rapidly when exposed to low temperatures. Mice with the obese hyperglycemic syndrome show considerably hypertrophied islets of Langerhans, both as concerns alpha and beta cells,[44] an increased pancreatic insulin[45] and glucagon[46] content, which supports a previously postulated etiology[44] of primary pancreatic dysfunction, namely increased insulin secretion and probably increased glucagon secretion. Such an etiology is supported by the fact that obese hyperglycemic mice show a sixfold increase in the rate of hepatic glycogen turnover[47] and in hepatic phosphorylase activity.[48] (Glucagon is known to activate hepatic phosphorylase.) Of particularly critical importance in the definition of "metabolic" obesity are the facts that in this syndrome, fasted rates of lipogenesis are increased over the fasted normal rates[37-39, 49] and reducing the animals to normal weight by underfeeding them does not bring body composition back to normal, but leaves them with a fat content still considerably increased over the normal at the expense of non-fat tissues.[8, 30]

It is particularly interesting to note that another type of genetic obesity in mice, also associated with hyperglycemia has been described recently by workers in New Zealand.[34] These "NZO mice" exhibit a syndrome which, in spite of certain resemblances, is different from the hereditary obese-hyperglycemic syndrome studied in your lecturer's laboratory. In particular these animals mate and produce offspring (instead of having to be obtained by mating of non-obese carriers of the obese gene or by artificial insemination or ovum transplantation). Extensive metabolic studies have not yet been published but reaction of the blood glucose level to fasting appears quite different in these animals: the usually high blood sugar levels of NZO mice may go even higher during a fast instead of going down rapidly when food is withdrawn as in the hereditary obese hyperglycemic syndrome. In the

NZO mice low glucose values are observed during pregnancy, and very low values at parturition. Like the hereditarily obese hyperglycemic mice, the NZO mice show insulin resistance.

Mice made obese by grafting ACTH secreting tumors show a number of metabolic abnormalities. Blood glucose levels are high in some animals. The blood sugars of all such mice show a remarkable stability under fasting conditions. Liver glycogen levels also remain higher than normal under fasting conditions, doubtless reflecting more active gluconeogenesis because of increase in circulating corticosteroids.[41] Hepatic glucose–6–phosphatase activity is increased (while phosphorylase activity is normal, unlike the finding in the obese hyperglycemic syndrome[41]). As in other forms of metabolic obesity (and characteristic of the class), the fasted rate of lipogenesis is greater than the normal fasted rate.[42] When these animals are reduced to normal weight, their fat content is still much higher than normal,[36] another typical feature of metabolic obesities.

Behavioral studies also emphasize the difference between "regulatory" and "metabolic" obesities in mice.[50, 51] Regulatory and metabolic types react differently to different diets.[8] Similarly, the association with pathological conditions differs between the two classes.[8] This has been analyzed, as regards the complex interrelationships between various types of obesity and diabetes, in a recent review on hyperglycemia.[2]

Finally, it may be worthy of mention that the distinction between "regulatory" and "metabolic" pathogenesis has been extended to anorexias and to the mode of action of anorexigenic drugs,[8] and has been used as a basis for the experimental analysis of the mechanism of anorexia in certain deficiencies.[52]

Limitation of Normal Regulation Leading to Obesity

Allusion has already been made to the fact that under conditions of reduced output, the regulation of food intake may become very imprecise. A corollary is that when otherwise normal animals are placed under outlandish conditions the regulation of food intake may not adjust any more their intake to their energy output. Such a situation is encountered when animals are caged or their movements otherwise restricted;[53] or in man, when activity is decreased to extremely low levels.[54-56] It is also encountered in certain strains of animals when these are fed a ration abnormally high in fat.[35, 57]

Extension of These Concepts to Man

A description of genetic, traumatic and environmental factors leading to obesity in man has been given at length in a previous review[7] and forms of obesity classified according to these etiological concepts are given in Table I.

Literal extension of the examples worked out in the mouse or other experimental animals to man is not possible, though there are indications that the overweight, middle age, non-ketotic type of diabetes in human subjects may be analogous to the hereditary obese hyperglycemic syndrome of mice. On the other hand, extension to man of the general concept of the existence of "regulatory" and "metabolic" hyperphagias (or anorexias) appears legitimate. For example, psychogenic obesities would be generally regulatory; endocrine obesities, metabolic. Such a distinction between these two classes plus the multiplicity of types within each class leads one to expect that obese patients may exhibit different reactions to the same treatment; in particular it may explain why certain patients find it easier to stay on certain reducing diets, others on diets of almost inverse composition.

Finally, considerable evidence has been adduced that in man, too, the range of adaptation of normal regulation does not cover the complete range of possible energy expenditures; in adult man at very low activity ranges, appetite does not decrease in proportion to caloric output, with resultant accumulation of fat.[54] In adolescents, obesity is more characteristically associated with inactivity than with intakes much in excess of normal.[55] Conversely, vigorously exercising obese adolescents results in decrease of their fat content even when no attempt is made to control intake.[56] These facts may be of particular importance in view of the prevalence of obesity in the school population.[58]

Practical Suggestions

Your speaker concluded a review published in a British scientific journal two years ago[8] with some practical suggestions resulting from experience gained in several years of studying the problems of obesity. In a lecture given under the auspices of the Public Health Committee of the Academy and before an audience which includes many practicing physicians engaged in the treatment of obesity, it may be useful

to reiterate these suggestions; especially since the journal in which they originally appeared may not be generally available to this audience.

General Attitude of the Therapist. Obesity is not a moral issue. It is a medical problem, complex and little understood. Censorious comments, sermons, and the shifting of the entire responsibility on to the patient are neither proper nor effective.

Diagnosis of Obesity. Blind application of height-weight tables is unscientific. The principles underlying the construction of these tables have been ably criticized by Keys.[59] In practice, extreme deviations from the average are obvious. Small deviations cannot be interpreted without examination of the patient for muscle development. The old-fashioned pinching method is a cheap and simple substitute for underwater weighing, measurement of thiocyanate or deuterium space, and the like.

Inducements to the Patient. "Scare" propaganda is one of the curses of the modern world. Though the association of obesity with increased mortality and morbidity risks is established, distinction between association and causation is not always clear. There is enough evidence to justify reduction programs to promote health as well as on esthetic grounds, but there are dangers in threats as well as in excessive promises of reward. This has been particularly emphasized by Bruch (personal communication) as regards children.

Informing and Misinforming the Patient. It is necessary to inform the patient about the first law of thermodynamics, and about the calorie value of foods. The importance of the latter cannot be overemphasized. Sound knowledge of the calorie value of foods will not only guide the patient during treatment, it will also protect him against the dishonest claims of manufacturers of "miracle foods" (such as "low calorie bread"). It is wrong and dangerous to belittle the influence of genes or exercise.

Use of Hereditary Data. It has been repeatedly shown (see above) that obesity runs in families, with genetic as well as environmental factors involved. Studies in the United States have shown that less than 10 per cent of the children of parents of normal weight are obese, but that the proportion rises to 50 per cent if one parent is obese and to 80 per cent if both parents are obese. Studies of identical and fraternal twins have shown that food habits are not the main factor. Instead of denying the facts of heredity it would be more intelligent and effective to use them to detect other overweight persons and, more

important, to try to prevent the development of obesity in susceptible children. Obesity is most malignant when the onset is early.

Exercise. Natural selection, operating for hundreds of thousands of years, made men active, resourceful creatures, well prepared to be hunters, fishermen or farmers. The mechanism regulating food intake was not adapted to the highly mechanized conditions of modern life, any more than animals were evolved to live in a cage. In many cases adaptation to modern conditions without development of obesity implies that the person will have either to step up his activity or endure mild or acute hunger all his life. The first alternative is difficult, especially in the United States and Canada, where the cities offer little inducement to walking and are often poorly provided with facilities for adult exercise. Even among the young, highly competitive sports for the few are often emphasized at the expense of individual sports which all could learn and continue to enjoy after school and college years are over. If the first alternative, stepping up activity is difficult, it is well to remember that the second alternative, lifetime hunger, is so much more difficult that to rely on it for weight control in cases of sedentary overweight can only continue to produce the fiascos of the past. Strenuous exercise on an irregular basis, in untrained persons already obese, is obviously not what is advocated here. But a re-organization of one's life to include regular exercise adapted to one's physical capacity is a sound preventive measure and a justified return to the wisdom of the ages. Moderate exercise during weight reduction, when practicable, also helps in promoting nitrogen balance and muscle tone.

Diets. The essential principle to follow in devising the diets is that a good reducing diet is one on which the patient does not feel too hungry. The diversity of probable etiologies makes it likely that different patients will feel more comfortable on different types of diet. In practice, the choice of foods by obese individuals and their feeding patterns are as diverse as in normal subjects.[60] Judging from literature reports, it appears that successful weight reduction has been observed on high fat, low carbohydrate diets; on high protein, low fat diets; on high protein, moderate fat diets; on low protein diets; on diets of average composition where calories have been cut down without changes in the proportion of nutrients. On the other hand, it has been repeatedly found[61-63] that most obese patients tend to do their overeating late in the day and at night, which indicates that evening eating should be

controlled with particular care. Diet prescription should be an individual operation, adapted to the patient's rate of energy expenditure and the desired rate of weight loss. It should furnish an opportunity for education in the calorie value of foods. It should also permit nutrition education in general. Finally, it should be experimental; trial and error will permit the finding of the most effective diet, as well as the most suitable schedule of exercise. "Fad" diets may have a short-term value but they have no lasting educational or practical worth. If, as some have claimed, it is possible to "shrink the stomach" or "re-train the appetite", special diets might perhaps be used for that purpose before a change is made to a more normal diet. The evidence offered in favor of the process is, however, very scanty. In some cases, better success is obtained with smaller and more frequent meals. The practice of eating slowly seems desirable on physiological grounds, since satiety mechanisms are likely to need time to take effect; it is desirable on psychological grounds also.

Obesity in Childhood and Pregnancy. It seems undesirable as a rule to attempt to reduce weight in children or pregnant women. A better solution consists in keeping the child's or the pregnant woman's weight at its existing value and letting the child "grow up" to the weight or letting postpartum weight loss achieve at least part of the desired result in the pregnant woman. It is important to remember, when dealing with obesity in childhood, that inactivity may be the major cause and that it may be easier and more effective to step up activity than to reduce food intake. Care must be exercised, particularly with children obese since their youth, not to do more harm than good; with present methods, the prognosis for such subjects is generally poor and the psychological trauma of persistent and tactless attempts at reduction may be considerable.

Limitations of Potential Success. It ought to be more generally recognized that present-day methods are ineffective with many individuals. With some patients, psychiatrists feel that attempts at weight reduction may be undesirable in the absence of a complete physiological and psychological investigation which may be out of the question. Ohlson and associates[63] showed that a certain type of obese patient is invariably thrown into negative nitrogen balance on reducing diets, even of the high-protein variety, and that the weight of this type of obese patient returns rapidly to its original level when the period of

treatment is over. In general, few problems are more important in this field than the typing of obese patients as regards their anthropometric, metabolic and psychological characteristics. Modes of response to different treatments are doubtless related to the nature of the abnormalities which had led to obesity.

REFERENCES

1. Hundley, J. H. Need for weight control programs, in *Weight control;* A collection of papers presented at the Weight Control Coloquium, Iowa State College, Ames, Iowa, Iowa State College Press, 1955, chapt. 1, pp. 1-12.
2. Shull, K. H. and Mayer, J. Experimental hyperglycemic states not primarily due to a lack of insulin, *Vitamins and Hormones, 14:*187-226, 1956.
3. Kurlander, A. B., Abraham, S. and Rion, J. W. Obesity and disease, *Human Biol. 28:*203-16, 1956.
4. Keys, A. Weight changes and health of men, in *Weight control;* A collection of papers presented at the Weight Control Colloquium, Iowa State College, Ames, Iowa, Iowa State College Press, 1955, chapt. 8, pp. 108-118.
5. Brobeck, J. R. Neural factors in obesity, *Bull. N.Y. Acad. Med. 33:*762-70, 1957.
6. Hamburger, W. W. Psychological aspects of obesity, *Bull. N.Y. Acad. Med. 33:* 771-82, 1957.
7. Mayer, J. Genetic, traumatic and environmental factors in the etiology of obesity, *Physiol. Rev. 33:*472-508, 1953.
8. Mayer, J. The physiological basis of obseity and leanness, Parts I and II, *Nutrition Abstr. Revs. 25:*597-611, 871-83, 1955.
9. Anliker, J. and Mayer, J. An operant conditioning technique for studying feeding-fasting patterns in normal and obese mice, *J. appl. Physiol. 8:*667-70, 1956.
10. Mayer, J., French, R. G., Zighera, C. F. and Barnett, R. J. Hypothalamic obesity in the mouse: Production, description and metabolic characteristics, *Amer. J. Physiol. 182:*75-82, 1955.
11. Marshall, N. B., Barnett, R. J. and Mayer, J. Hypothalamic lesions in goldthioglucose injected mice, *Proc. Soc. exp. Biol. Med. 90:*240-44, 1955.
12. Anand, B. K. and Brobeck, J. R. Localization of a "feeding center" in the hypothalamus of the rat, *Proc. Soc. exp. Biol. Med. 77:*323-24, 1951.
13. Fregly, M. J., Marshall, N. B. and Mayer, J. The effect of changes in ambient temperature on spontaneous activity, food intake, and body weight of goldthioglucose obese and non-obese mice, *Amer. J. Physiol. 188:*435-38, 1957.
14. Marshall, N. B. and Mayer, J. Energy balance in goldthioglucose obesity, *Amer. J. Physiol. 178:*271-74, 1954.
15. Morrison, S. D. and Mayer, J. Adipsia as a primary effect of lateral hypothalamic lesions in rats (abstract), *Fed. Proc. 16:*90-91, 1957.
16. Teitelbaum, P. and Stellar, E. Recovery from the failure to eat produced by hypothalamic lesions, *Science 120:*894-95, 1954.
17. Strominger, J. L. and Brobeck, J. R. A mechanism of regulation of food intake, *Yale J. Biol. Med. 25:*383-90, 1953.
18. Brobeck, J. R. Neural regulation of food intake, *Ann. N.Y. Acad. Sci. 63:* 44-55, 1955.
19. Soulairac, A. La physiologie d'un comportement: L'Appetit glucidique et sa régulation neuro-endocrinienne chez les rongeurs, *Bull. Biol. France, Belgique, 81:*274-432, 1947.
20. Mayer, J. and Yanonni, C. Z. Increased intestinal absorption of glucose in three forms of obesity in the mouse, *Amer. J. Physiol. 185:*49-53, 1956.
21. Van Itallie, T. B., Beaudoin, R. and Mayer, J. Arteriovenous glucose differences, metabolic hypoglycemia and food intake in man, *J. clin. Nutrition 1:*208-

17, 1953.

22. Stunkard, A. J. and Wolff, H. G. Correlation of arteriovenous glucose differences, gastric hunger contractions and the experience of hunger in man (abstract), *Fed. Proc. 13:*147, 1954.
23. Bernstein, L. M. and Grossman, M. I. An experimental test of the glucostatic theory of regulation of food intake, *J. clin. Invest. 35:*627-33, 1956.
24. Stunkard, A. J. and Wolff, H. G. Studies on the physiology of hunger. I. The effect of intravenous administration of glucose on gastric hunger contractions in man, *J. clin. Invest. 35:*954-63, 1956.
25. Stunkard, A. J., Van Itallie, T. B. and Reis, B. B. The mechanism of satiety: effect of glucagon on gastric hunger contractions in man. *Proc. Soc. exp. Biol. Med. 89:*258-61, 1955.
26. Stunkard, A. J. Studies on the physiology of hunger. II. The effect of intravenous administration of various nutrients on the gastric hunger contractions of a man with severe brain damage. Presented at the Symposium of "Nutrition and Behavior," Minneapolis, 1956, *Amer. J. clin. Nutrition 5:*203-11, 1957.
27. Van Itallie, T. B. and others. Unpublished results.
28. Mayer, J. and Marshall, N. B. Specificity of goldthioglucose for ventromedial hypothalamic lesions and obesity, *Nature 178:*1399-1400, 1956.
29. Forssberg, A. and Larsson, S. On the hypothalamic organization of the nervous mechanism regulating food intake. Part II. Studies of isotope distribution and chemical composition in the hypothalamic region of hungry and fed rats, *Acta Physiol. scand. 32,* suppl. 115:41-59, 1954.
30. Gasnier, A. and Mayer, A. Recherches sur la régulation de la nutrition, *Ann. Physiol. Physicochim. Biol. 15:*145-214, 1939.
31. Mayer, J. Regulation of energy intake and the body weight: The glucostatic theory and the lipostatic hypothesis, *Ann. N. Y. Acad. Sci. 63:*15-43, 1955.
32. Cowgill, G. R. The energy factor in relation to food intake: Experiments on the dog, *Amer. J. Physiol. 85:*45-64, 1928.
33. Mayer, J. and Vitale, J. J. Thermochemical efficiency of growth in rats, *Amer. J. Physiol. 189:*39-42, 1957.
34. Bielschowsky, M. and Bielschowsky, F. The New Zealand strain of obese mice: Their response to stilbestrol and to insulin, *Australian J. exp. Biol. med. Sci. 34:* 181-98, 1956.
35. Mikelson, O., Rakahashi, S. and Craig, C. Experimental obesity: Production of obesity in rats by feeding high fat diets, *J. Nutrition 57:*541-44, 1955.
36. Williams, D. R. and Teitelbaum, P. The control of drinking behavior by means of an operant-conditioning technique, *Science, 124:*1294-97, 1956.
37. Bates, M. W., Zomzely, C. and Mayer, J. Fat metabolism in three forms of experimental obesity. IV. Instantaneous rates of lipogenesis *in vivo, Amer. J. Physiol. 181:*187-90, 1955.
38. Mayer, J., Hagman, N. C., Marshall, N. B. and Stoops, A. J. Fat metabolism in three forms of experimental obesity. V. Hepatic lipogenesis *in vitro, Amer. J. Physiol. 181:*501-03, 1955.
39. Mayer, J. and Zighera, C. Y. Fat metabolism in various forms of obesity. VI. Instantaneous lipogenesis in hypothalamic obese mice, *Experientia 11:* 358-59, 1955.
40. Mayer, J. Regulation of food intake and the multiple etiology of obesity, in *Weight control:* A collection of papers presented at the Weight Control Colloquium, Iowa State College, Iowa State College Press, 1955, chapt. 3, pp. 29-48.
41. Shull, K. H., Cahill, G., Gadsen, E. and Mayer, J. Glucose-6-Phosphatase and phosphorylase activities in mice bearing ACTH secreting tumors, *J. biol. Chem. 222:*415-20, 1956.
42. Zomzely, C. and Mayer, J. Fat metabolism in various forms of obesity. VII. Lipogenesis and cholesterogenesis in mice with adrenotropic pituitary tumors, *Amer. J. Physiol. 187:*365-68, 1956.
43. Mayer, J., Zomzely, C. and Furth, J. Body composition and energetics in obesity induced in mice by adrenotropic tumors, *Science 123:*184-85, 1956.

44. Mayer, J., Andrus, S. B. and Silides, D. J. Effect of diethyldithiocarbamate and other agents on mice with the obese-hyperglycemic syndrome, *Endocrinology 53*:572-81, 1953.
45. Wrenshall, B. A., Andrus, S. B. and Mayer, J. High levels of pancreatic insulin, coexistent with hyperplasia and degranulation of beta cells in mice with the hereditary obese-hyperglycemic syndrome, *Endocrinology 56*:335-40, 1955.
46. Wrenshall, B. A., Clarke, D. W. and Mayer, J. Effects of pituitary growth hormone on the insulin and HGF extractable from the pancreas of the obese-hyperglycemic mouse, *Nature 177*:1235, 1956.
47. Shull, K. H. and Mayer, J. The turnover of liver glycogen in obese-hyperglycemic mice, *J. biol. Chem. 218*:885-96, 1956.
48. Shull, K. H., Ashmore, J. and Mayer, J. Hexokinase, glucose-6-phosphatase and phosphorylase levels in hereditarily obese-hyperglycemic mice, *Arch. Biochem. Biophys. 62*:210-16, 1956.
49. Silides, D. J. and Mayer, J. Effect of hormonal and dietary treatment on lipogenesis from acetate in hereditarily obese-hyperglycemic mice, *Experientia 12*:66-71, 1956.
50. Alonso, L. G. and Maren, T. H. Effect of food restriction on body composition of hereditary obese mice, *Amer. J. Physiol. 183*:284-90, 1955.
51. Anliker, J. and Mayer, J. The regulation of food intake: Some experiments relating behavioral, metabolic and morphologic aspects; in Symposium on Nutrition and Behavior, Minneapolis, 1956. *Amer. J. clin. Nutrition 5*:148-53, 1957.
52. Agnew, L.R.C. and Mayer, J. Mechanism of anorexia in vitamin deficient hyperphagic animals, *Nature. 177*:1235-36, 1956.
53. Mayer, J. and others. Exercise, food intake and body weight in normal rats and genetically obese adult mice, *Amer. J. Physiol. 177*:544-48, 1954.
54. Mayer, J., Roy, P. and Mitra, K. P. Relation between caloric intake, body weight and physical work in an industrial male population in West Bengal, *Amer. J. clin. Nutrition 4*:169-75, 1956.
55. Johnson, M. L., Burke, B. S. and Mayer, J. Relative importance of inactivity and overeating in the energy balance of obese high school girls, *Amer. J. clin. Nutrition 4*:37-44, 1956.
56. Heald, F., Sorensen, A. and Mayer, J. Effect of enforced exercise on obese and normal-weight adolescent boys. To be submitted for publication.
57. Fenton, P. F. and Dowling, M. T. Nutritional obesity in mice, *J. Nutrition 49*:319-31, 1953.
58. Johnson, M. L., Burke, B. S. and Mayer. J. The prevalence and incidence of obesity in a cross-section of elementary and secondary school children, *Amer. J. clin. Nutrition 4*:231-38, 1956.
59. Keys, A. Body composition and its change with age and diet, in *Weight control*: A collection of papers presented at the Weight Control Colloquium, Iowa State College, Ames, Iowa, Iowa State College Press, 1955, chapt. 2, pp. 18-28.
60. Beaudoin, R. and Mayer, J. Food intake of obese and non-obese women, *J. Amer. dietet. Assoc. 29*:29-33, 1953.
61. Dole, V. P. and others. Treatment of obesity with a low protein, calorically unrestricted diet, *Amer. J. clin. Nutrition 2*:381-91, 1954.
62. Stunkard, A. J., Grace, W. J. and Wolff, H. G. The night-eating syndrome, *Amer. J. Med. 19*:78-86, 1955.
63. Ohlson, M. A. and others. Weight control through nutritionally adequate diets, in *Weight control*: A collection of papers presented at the Weight Control Colloquium. Iowa State College, Ames, Iowa, Iowa State College Press, 1955, chapt. 15, pp. 170-87.

NEURAL FACTORS IN OBESITY*

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OBESITY is always the result of an imbalance between energy intake and energy expenditure, where intake exceeds expenditure over a period long enough to allow energy to accumulate as excess fat. Thus, obesity is a token of some long-standing error in regulation of energy exchange. In adult animals or man there are only a few types of error that can cause obesity, since in addition to body weight only three factors are involved in energy exchange. Food is the only source of energy, while heat production and work output are the only avenues of expenditure (excluding storage as fat); gain of weight is possible only when food is greater than heat and work, combined. The fact that most of us preserve a fairly stable body weight is evidence for the precision of the regulation of these variables, but an exact balance is not always maintained, even in normal individuals, and a gain of weight and even a true obesity can sometimes be induced merely by altering the composition of the diet or environmental conditions.

In my opinion there is no conclusive evidence that body weight is regulated as such, although there are many data which indicate that it is controlled indirectly through regulation of the other three variables. Food intake, heat loss, and exercise, however, are definitely regulated. If the regulations are set so that intake exceeds heat loss and exercise, weight gain invariably occurs until a new equilibrium state is reached at a larger body mass; or if food be less than heat production and work, the body loses weight and stabilizes at a new, lower level unless the animal dies first from starvation. Neither the regulation of heat loss nor that of exercise is directed toward the maintenance of a constant weight. That is, an animal will not maintain a lower body temperature to conserve mass, nor will it (short of starvation) reduce activity to preserve weight or weight gain. It follows, therefore, that

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whenever body weight is constant in spite of variations in heat loss or activity, this constancy represents a proportional variation in food intake which often, but not invariably, changes in proportion to energy output.

All of these adjustments and variations come ultimately from the central nervous system. Many levels of the brain take part—from peripheral nerves to highest levels of the cortex. The higher the level in the neuro-axis, the more complicated the integration. Since the cerebral cortex is the highest level, it is assumed to be responsible for the most elaborate phenomena, for the influence of habit, prejudice, and emotional states as they affect energy exchange, as well as for selection or preferences among the variables. Possibly the cortex acts through the hypothalamus, but it may very well act directly upon lower centers, even at a reflex level. Interactions between the cerebral cortex and these lower mechanisms may be related to the psychiatric factors important in the genesis of obesity.

The level of the nervous system most definitely known to be associated with obesity is the hypothalamus. Lesions here lead to an obesity that is caused mainly by increased food intake or hyperphagia. Yet other variables of energy exchange are also regulated by this part of the brain, and selected lesions may disturb regulation of body temperature, including both heat production and heat loss, may affect the animal's motor output or its sleep-waking cycle. Since the hypothalamus appears to be capable of modifying every one of the factors in energy exchange, it has come to be regarded as the region that integrates these variables into patterns of regulation. The stabilization of body weight seen in most normal adult individuals is one such pattern of regulation.

Before going further with this subject, may I review briefly some of the interrelationships among the several variables of energy exchange. In laboratory animals one can arrange experiments to demonstrate what happens to food intake, activity, and body weight, for example, when heat loss is altered by warming or cooling the environment. Or changes in activity and weight can be recorded when food intake is changed. Many of the experiments illustrated in the accompanying figures were designed to study these relationships with reference to one particular hypothesis of the nature of the regulation. This hypothesis, proposed in 1948,[1] is that "both food and work represent important sources of heat for the organism, and the amount of food

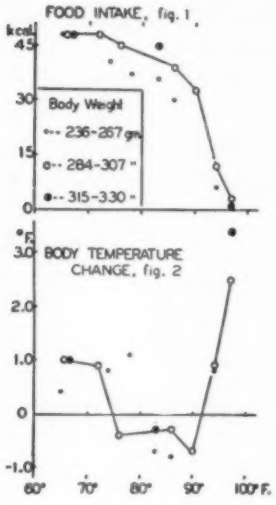

Fig. 1.

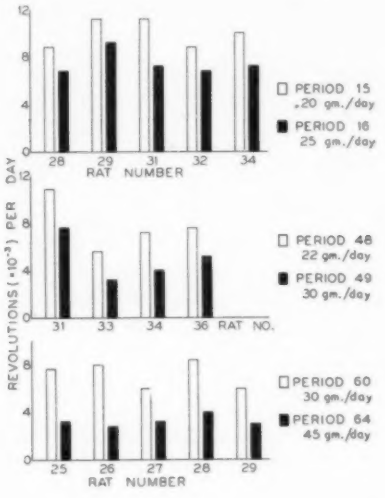

Fig. 2.

Figure 1. Food intake (upper graph) and body temperature change (lower graph) of rats exposed to selected environmental temperatures for 18 hours. Where heating induced fever, food intake was low or even absent. (From Brobeck[1], reprinted by permission.)

Figure 2. Spontaneous locomotor activity of rats fed selected amounts of food. Activity was always less on the larger food intake.

eaten or muscular activity undertaken is determined in part by the animal's need for heat and its ability to lose heat to the environment". I shall not attempt in a few words here to verify this hypothesis, although it may serve as a guide to the interpretation of certain of the experiments now to be described. A more extensive account is found in a paper now in press elsewhere.[2]

The experiment summarized in Figure 1 was performed by measuring food intake and body temperature in rats exposed for 18 hours to any one of a series of temperatures ranging from 65° to 97°F. At the cooler temperatures the animals ate a large amount of food, and experienced a slight rise in body temperature, probably because they were more active at the end than at the beginning of the experiment. At intermediate temperatures food intake was less, and the final body temperature was lower than the initial one. When the room temperature was above 90°, however, food intake was negligible; here the rats were beginning to have a true fever. At 94°F. room temperature their

body temperatures were comparable to those at 65°F., but food intake was much less in the hot than in the cooler environment. At 97°F. they ate nothing, and had fevers averaging about 2.5°F. above resting values. The data show that animals eat more in a cool and less in a warm environment, and that if the room is hot enough so that they are unable to prevent a fever, they will not eat at all.

Figure 2 shows the nature of the correlation between food intake and spontaneous activity. Here the rats were given arbitrarily chosen amounts of food, differing in the three different experiments of the series. In each of the three experiments the food intake was limited at first, then increased by a fixed amount. All of the data show that activity decreases when the available food is increased, or, stated differently, that limitation of food is accompanied by increased activity, while ad libitum feeding tends to reduce the activity. Under natural conditions this mechanism serving to increase activity when food is limited is obviously important to the animal as a method for finding more food. It is not a learned response, since it can be observed also under laboratory conditions in rats that have never been given an opportunity to migrate in search of food. It seems to represent an innate behavior in this particular situation. A similar type of response is shown in Figure 3, where food intake was constant during changes in room temperature. The animals in this experiment ran less at warmer temperatures, more when the room was cool. Stevenson[3] has studied these relationships more thoroughly, and one of his figures includes data from food intake, activity, and temperature all in one experiment. He found that in animals fed ad libitum there was a slight but definite increase in activity as room temperature was lowered (Fig. 4). In animals not fed for four days, activity in the cold was more than six times greater than in similar rats fasted at 33°C. But when the fasting experiment was performed with rats acclimatized to cold, the activity in the cold environment, though definitely increased, was significantly less than in non-acclimatized rats at the same temperature.

All of these experiments, as Stevenson has noted, are consistent with the hypothesis that the conditions of temperature regulation are important in regulation of activity as well as food intake. The regulation is sometimes set so as to disturb further the energy balance. Thus, when the room is cool or food is limited, animals spend energy for extra activity even though they hasten by this process the exhaustion of their

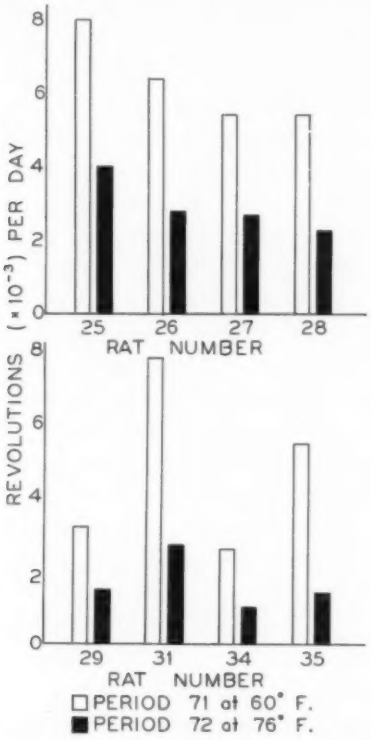

Figure 3. Activity of rats on constant feeding at two different environmental temperatures. Activity was less at warmer temperature.

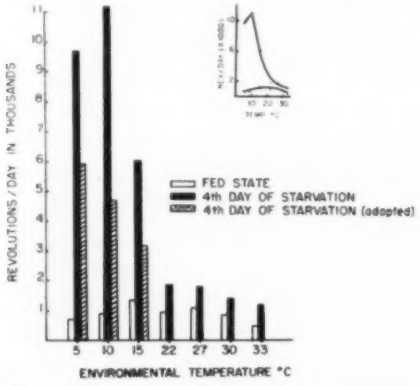

Figure 4. Effect of starvation and a cold environment upon spontaneous activity of rats. (From Stevenson[8], reprinted by permission.)

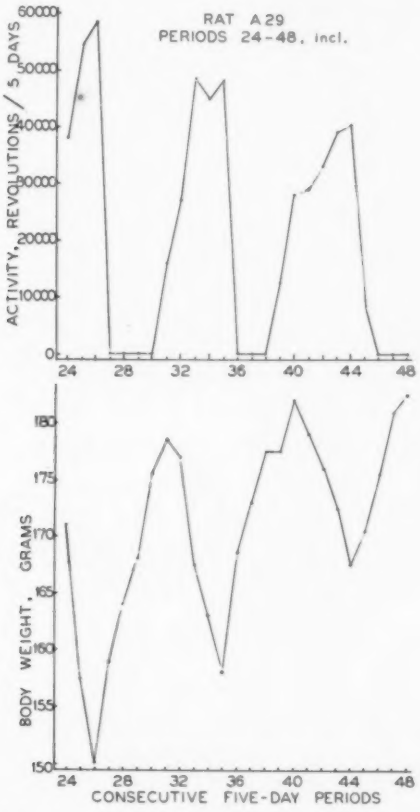

Figure 5. Activity and weight gain of rat fed constant amount of food. When cage was blocked to prevent running, rat gained weight, but when running was permitted, the animal ran so much that body weight fell.

energy reserves (Fig. 5). If the room is warm, they fail to eat even though they lose weight because of the energy deficit. If the goal of the regulations were energy balance, these responses would be paradoxical ones. But if the more immediate basis of the regulation is the maintenance of body temperature, then the responses are appropriate to the circumstances. Energy balance, if it is to be achieved, requires other types of adjustments. Under the conditions of these experiments where other compensations were not available to the animals, the common denominator of temperature regulation becomes emphasized.

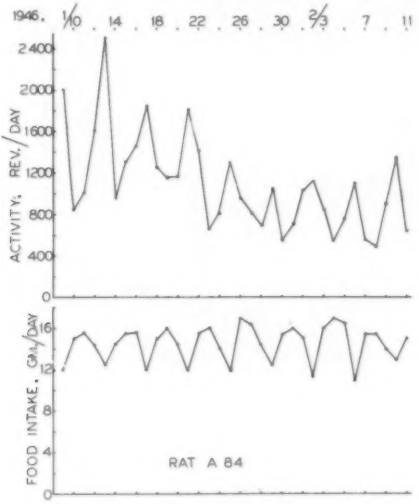

Figure 6. Estral cycles of running and food intake. Intake was low at estrus when activity was high. (From Brobeck and others.[4])

One other type of evidence for the regulation of energy exchange may be reviewed, in this instance by utilizing the estrous cycle as a means of demonstrating variations. When female rats are in estrus, their activity is significantly increased (for references, please refer to Brobeck, Wheatland and Strominger[4]) and since estrus recurs every four to five days, the activity cycle is an obvious picture of the estral cycle. Knowing that these large variations in activity occur, experiments were undertaken to learn whether there are also cycles in the other variables, food intake, body temperature, and body weight. The presence of these other cycles is shown in Figures 6, 7 and 8. Estral cycles, therefore, in addition to their more obvious features in reproductive behavior, are accompanied by variations in the conditions of energy exchange in which at the time of estrus the energy output is high and intake is low, while during di-estrus the output is low and intake is high. If the hypothalamus is involved in the control of the anterior pituitary gland and the gonads, as many investigators believe, these experiments appear to provide evidence that the hypothalamus is an integrator of sexual cycles and energy exchange.

More definite evidence that the hypothalamus is the regulator may

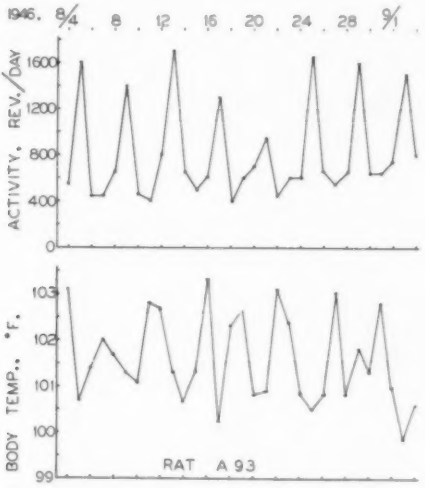

Figure 7. Estral cycles of running and body temperature.

be obtained from studies on animals with hypothalamic lesions. Of the many reports describing these animals, I shall select only one, that of Anand, whose data show the dual nature of hypothalamic control of feeding.[5] Anand found that, whereas lesions in the medial portion of the hypothalamus lead to overeating and obesity, as other investigators had noted before him, lesions situated more laterally bring about a failure of feeding or aphagia which persists in many cases until death. Anand's data, and similar reports from other laboratories, point up the importance of the hypothalamus in regulation of food intake—a particular phase of regulation of energy exchange. Other data suggest a similar regulation of body temperature and activity, but only those relating to food intake are included here because of the obvious correlation between hyperphagia and obesity. There is also evidence for combined deficits of regulation, including Hetherington's observations that fat animals are less active than normal,[6] and our own finding that some rats with hypothalamic lesions outgain the controls with which they are pair fed. The purpose of this symposium is to discuss obesity, however, rather than these regulations, and this paper is presented as a reminder that obesity is caused by an imbalance of energy exchange, that lesions in the hypothalamus may alter the energy exchange, and

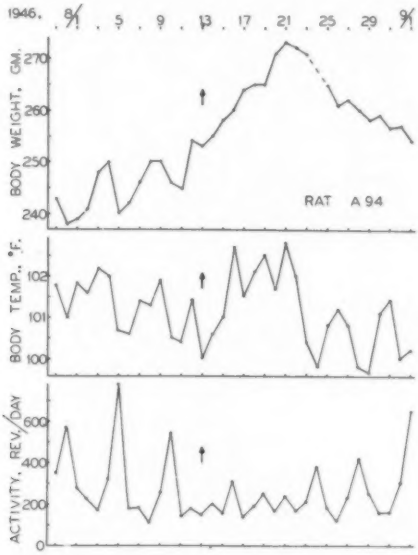

Figure 8. Cycles of running, body temperature, and body weight, including a period of pseudo-pregnancy beginning at the arrow.

that when obesity follows such lesions, it is caused primarily by an increase of energy intake—by hyperphagia.

This review should not imply that the neural regulation of energy exchange is thoroughly understood; many points of uncertainty remain. Nevertheless, it appears that adequate methods are now available for further research, together with appropriate hypotheses for testing by these methods. As these regulations are better understood, the nature of the abnormalities leading to obesity in human subjects becomes apparent and provides a basis for more successful diagnosis and treatment of this condition.

REFERENCES

1. Brobeck, J. R. Food intake as a mechanism of temperature regulation, *Yale J. Biol. Med. 20*:545-52, 1948.
2. Brobeck, J. R. Neural control of hunger, appetite and satiety, *Yale J. Biol. Med.* 1957, in press.
3. Stevenson, J. A. F. *Diet and survival*, Josiah Macy, Jr. Foundation, Cold injury, Third Conference, 1954, pp. 165-168.
4. Brobeck, J. R., Wheatland, M. and Strominger, J. L. Variations in regulation of energy exchange associated with estrus, diestrus and pseudopregnancy in rats, *Endocrinology 40*:65-72, 1947.
5. Anand, B. K. and Brobeck, J. R. Hypothalamic control of food intake in rats and cats, *Yale J. Biol. Med. 24*:123-40, 1951.
6. Hetherington, A. W. and Ranson, S. W. The spontaneous activity and food intake of rats with hypothalamic lesions, *Amer. J. Physiol. 136*:609-17, 1942.

PSYCHOLOGICAL ASPECTS OF OBESITY*

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IT HAS become the vogue in recent years to include a psychiatrist on panels discussing obesity. I am delighted to be the one invited this evening to join the distinguished investigators in this symposium honoring the memory of Doctor Augustus Walter Suiter. Having read of Dr. Suiter's abiding interest in Public Health and Preventive Medicine in New York State and in the nation,[1,2] I am sure he would be pleased with our subject tonight, representing as it does, one of our major public health problems. However, I have been trying to think through the essential meaning of psychiatric participation in this topic. I hope it is not just a fad. Actually I think there are several pertinent reasons.

First, the psychiatrist is that medical clinician who is focussed on the behavior of man and the forces, both rational and irrational, which motivate behavior. Eating behavior can rightfully be included in this sphere of observation. The eating behavior of the obese, be he man or mouse, represents an excess of food intake beyond caloric requirements. I am sure Doctors Mayer and Brobeck will agree with me that hyperphagia (over-eating) is a necessary, although not sufficient factor, in the development of obesity in all species. The psychiatrist knows from his clinical work that similar behavior may have many different meanings and motivations. We have conventionally assumed that eating is always for nutritional purposes. Eating for such purposes is then logical and rational behavior. Preliminary psychiatric observations in human obesity suggest a first hypothesis that some of the hyperphagia is for non-nutritional purposes. Hence this type of eating appears to be illogical or irrational behavior. By this I simply mean that the reasons for non-nutritional eating may not be immediately apparent to either the patient or his physician. Modern psychiatrists also know from their work that behavior which may appear to be inappropriate, does indeed

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have a purpose and logic, when we can ferret out the hidden meanings by appropriate study. The need to examine this first hypothesis concerning non-nutritional eating is one reason why psychiatric participation may make a contribution to the understanding of the syndrome of obesity.

A second reason for psychiatric participation is the fact that both hunger and appetite are feeling states or psychological experiences which lead the organism to the purposeful motor act of eating. Nutritionists, biochemists and physiologists, though well aware of this, have sometimes shied away from its implications on the ground that such feeling states are subjective, vague or downright unscientific. I couldn't agree with them more that the study and understanding of sensations and perceptions is still fuzzy and as yet unprecise. Nevertheless, we cannot afford to be like the intoxicated man who was hunting for his door key under a street light when a passer-by got down on his knees to help him. "But," the inebriant protested, "I lost my key over there," pointing to a darkened doorway. "Why in the world, then, are you searching here?" asked the good Samaritan. "Because," came the reply, "this is where the light is." Scientifically dim as the field of perceptions may be, we may yet find some keys to the problem of obesity, if investigators interested in perception, emotions and motivations will turn their attention to this problem. Until the recent past, psychiatric observations of obesity have been largely random and single case reports. A noteworthy exception has been Dr. Hilde Bruch of this city, whose systematic studies of obesity in children[3-10] have already shed considerable light on certain psychological factors. Another persistent searcher and researcher is Dr. Albert Stunkard[11-15] of the Cornell University Medical College. Such investigators and other newer recruits in the field, like myself, are constantly striving to perfect better and more precise tools of inquiry.

A third reason for psychiatric participation relates to species differences in the obesity syndrome. I am convinced that to adequately understand obesity in man, we must study man. Laboratory observations on the mouse, the rat, the cat, dog and monkey have produced valuable metabolic and biochemical information which may indeed be applicable to man. With respect to species differences in perceptions and emotions, however, the human animal is unique. This is so, at least in part, because of man's unique cerebral cortical development.

This evolutionary structure allows for a psychic elaboration and distortion of sensations, including hunger and appetite, which requires psychiatric collaboration in research on human obesity.

Now that I have attempted to justify my presence, I wish first to tackle the topic of hunger and appetite. I want to emphasize the distinction between hunger and appetite. On this subject, I commend to you the thoughtful 1949 article by Janowitz and Grossman.[16] My views are in considerable accord with theirs and that is, of course, the reason why I like their article! With them, I regard hunger as resulting from disturbed biochemical, physiologic and nutritional equilibria within the body. When these internal disturbances reach a certain threshold, the individual perceives his hunger as an uncomfortable, even painful, set of feelings which leads him to replenish nutrients by eating. This behavior is nutritionally appropriate and therefore rational to all of us. We could say the purpose of such eating is to restore disturbed nutritional homeostasis. Nutritional homeostasis is maintained by multiple regulations at the cellular, hormonal, humoral and organ level. Such multiple factors of nutritional regulation seem to be analogous to those outlined for the regulation of body water by Dr. Edward Adolph of the University of Rochester School of Medicine.[17, 18] Light is gradually being shed on the specific regulatory mechanisms involved in nutritional homeostasis by such contributions as Dr. Mayer's on the arteriovenous blood glucose ratio in hunger and satiety[19] and by Dr. Brobeck on the regulatory functions of the ventro-medial and the lateral nuclei of the hypothalamus.[20] When such regulatory devices are disturbed, the individual perceives his hunger as both a psychic signal of this disturbed homeostasis and a nutritional drive to eat. This then is the adaptive cycle of hunger, eating and satiety. The perception of hunger, as emphasized by Janowitz and Grossman,[16] is an unlearned, unconditioned response to disturbed nutritional homeostasis. The simple proof for this is that the human newborn when hungry becomes restless, cries (as a signal) and after adequate feeding, relaxes and falls asleep. This is an unlearned model of adult eating as part of a readaptive nutritional cycle.

How does appetite differ? Appetite is a psychological desire to eat. It refers to a pleasurable anticipation; specifically, the relief through eating from the uncomfortable and painful feelings of hunger. Appetite is a learned experience. Appetite is first conditioned by the repetitive cycle of feeding experiences following hunger in infancy. This is the

earliest learning of appetite and I call it conditioning because it has some of the characteristics of reflex stimulus-response before the mental apparatus or mind is fully developed. I would imagine that the appetite of an infant conditioned on a strict four hour schedule would be of a different order than the appetite of an infant fed on self-demand. With the maturation of the mental apparatus, appetite involves the memory of satiety and the anticipation of future gratification from eating. The neonate who continues to cry until fed will, at 6 or 8 months, stop crying, if he hears his mother's step upon the stair or sees his formula being prepared. His budding psyche has learned to anticipate, and then to wait, for the pleasure of eating. This gratification is no longer purely nutritional satiety. It now involves the pleasurable anticipation of emotional gratification. This repetitive cycle of nutritional and emotional gratification becomes further associated with the person giving the food, usually the mother. This intimate association of being fed and being loved by the mother is of major significance in the developmental history of appetite. It is, incidentally, also of major importance in the child's learning to love another human being.

That appetite can be conditioned in childhood by feelings toward other people is given physiological support by recent experiments of Engel, Reichsman and Segal in "A Study of an Infant with a Gastric Fistula."[21] These authors found that the rate of total hydrochloric acid secretion in a 15-20 months old girl increased when she was relating to a loved person. When she withdrew from a stranger, the rate of total hydrochloric acid secretion fell. In other words, at this level of development, the baby's stomach was responding to a loved person in a similar physiologic way as to food.

In later childhood appetite takes on further emotional meanings as the association widens to include feelings toward home and other family members. Restaurant owners and food advertisers count on these ubiquitous associations to appetite when they advertise "Pies like mother used to make" or "Home Cooking." As learning proceeds, appetite takes on social meanings with friends and relatives outside the family. Certainly in adult life, eating together is connected with feelings of friendship, good fellowship and well being. Even extrafamilial economic and cultural factors can become involved with the child's appetite. Food to a family of marginal economic existence may become invested with feelings of security and community status. Similarly, religious beliefs

of the family and community which involve food, like the separation of meat and dairy products in the Orthodox Jewish household, may leave an indelible imprint on the development of appetite.

The child's appetite may also become invested with feelings stemming from conflict with his parents. Why do we joke about how many people dislike spinach? Is it because spinach doesn't taste good or did certain parents force their kids to eat it whether they were hungry or not? I know all of you have seen an angry child refuse to eat as a defiance of his parents. Some parents punish a child's misbehavior by depriving him of his meal or his dessert. Other parents offer ice cream and other prized foods as rewards or bribes for good behavior. Thus appetite that started out in response to the purely physiological experience of hunger, becomes invested with such diverse emotions as love and approval, defiance and the fear of punishment. By the time of adulthood, many of these emotional associations to appetite have been repressed into unconscious reservoirs of the mind.

In summary, adult appetite, in contrast to hunger, is a learned psychological experience. Appetite is intimately involved with a variety of emotions which stem primarily from early childhood experiences. It is folklore knowledge that strong emotions affect our appetite. Love, grief, excitement, disgust or fear may cause marked changes in appetite through such associations. Morbid emotional states, such as depressions, invariably produce a disturbance in appetite. This intimate association of appetite with emotions gives a rational explanation for a second psychiatric hypothesis, namely, some of the hyperphagia in human obesity is serving emotional needs (rather than nutritional). The individual patient may or may not be aware of this relation between his appetite and his emotions.

I would now like to turn to some of the clinical observations from which these psychiatric hypotheses are derived. A few years ago, with the help of some of my colleagues, I had the opportunity to study 18 obese men and women who were referred to psychiatry for therapeutic help.[22] Some were referred because they had failed to lose weight in the hands of the internist, endocrinologist and dietitian. This is the "end of the line" referral. Others were referred because of known emotional problems and were only incidentally obese. Therefore this was a selected group of obese patients. All had been studied from the physical standpoint and no organic pathology found pertinent to their obesity.

The focus was initially on therapy and only of investigative interest after I went back to gather up the psychologic data. The investigative instrument was the psychiatric interview, ranging from 1 to 398 periods. I can tell you at once that our therapeutic results, as far as weight loss, was far less rewarding than what we learned about these patients' hyperphagia.

I delineated four types of hyperphagia from this selected group of patients:

Group 1. *Overeating as a response to non-specific emotional tensions.* Ten patients stated they ate more than usual when tense or upset. They said when nervous, anxious, lonely, bored or blue a snack would in some way make them feel better—even, at times, when they had recently eaten a full meal. Some of these patients ate the most at night, as recently emphasized by Stunkard, Grace and Wolff as part of "the night eating syndrome."[12] The most frequently expressed emotional stimulus to eating was feeling blue, discouraged or depressed. I will return to this point shortly. Some patients promptly volunteered their observation of eating when emotionally upset. Others initially made no such connection but later in psychotherapy differentiated between eating when hungry and eating when upset.

Group 2. If a person can respond to a transient stimulus of grief, love, frustration or anger with eating, is it not logical that he might chronically overeat if the emotional stimulus continues over a long period of time? Such chronic overeating was indeed detectable in a second group of seven patients delineated as *overeating as a substitute gratification in intolerable life situations.* Let me give you an example from this second group:

Mr. W. H., a 45 year old business man had been overweight since childhood, as had his parents, suggesting a genic or constitutional factor in the development of his obesity. His usual weight was 190 lbs. Six years previously he had lost a steady job and had been in numerous businesses since, with financial worries and feelings of failure. During this period he gained weight up to 243 lbs. He had lost confidence in himself and his abilities. He was aware of daytime snacks and night raids on the ice box, even when he wasn't truly hungry. This kind of observation suggests that continuing emotional upsets, in this case worry, frustration and discouragement, may lead to hyperphagia and then weight gain, in a person predisposed genically or metabolically to

obesity. This involves a multifactorial interpretation of this man's obesity and is to be distinguished from any single cause approach, like psychogenesis.

Group 3. *Overeating as a symptom of an underlying emotional illness.* Eight patients fell in this group. Their overeating is more distinctly a symptom, apparently helping to prevent the outbreak of an underlying emotional illness. The underlying illnesses were mostly emotional depressions of varying proportions and several forms of hysteria. The following case happens to illustrate both of these underlying illnesses at different times in one patient's life.

Mrs. P. S. was a 38 year old married woman whose weight fluctuated up to 163 lbs. She was thin in childhood and weighed 95 lbs. at the time of her marriage. This woman revealed in psychiatric interviews, major emotional ties to both parents. She had been poorly prepared for adult feminine functions including marriage. She had not known about menstruation until her first period came, which upset her emotionally. She had little sex information and very few dates before marrying at age 19. She reluctantly accepted intercourse with her husband during the first three years of marriage, during which period her weight increased from 95 to 110 lbs. From that point on she was periodically frigid and many times refused to let her husband physically touch her. She gradually gained weight up to 150 lbs. She was able to lose weight by diet and amphetamine but at lower weights she was irritable, nervous, smoked excessively and feared becoming habituated to Dexedrine. At lower weights she was so nervous that she sometimes was afraid to stay alone in her house. This patient spontaneously observed that at lower weights she was more active physically and these were the periods when she would allow intercourse. At higher weights she felt phlegmatic, easily fatigued but less nervous. During these peaks of weight she would refuse intercourse. Psychiatrically speaking, this woman has an hysterical personality. I believe that periodically she handles her latent anxieties and prevents an outburst of full blown phobias by overeating. At higher weights she refuses intercourse which is emotionally upsetting to her.

Following the death of her beloved mother, this patient stated that she "cried for months" and was in bed a good part of this period. At one despondent point she turned on the oven gas with a suicidal intent. Frightened by this, she determined to use more will power and "pull

herself together" for the sake of her family. During this period she again overate to a peak of 163 lbs. when she no longer felt so despondent. This episode represents a reactive depression handled in part by her habitual hyperphagic response.

Here then is a woman with fluctuating weight from 110 to 163 pounds. She is as much predisposed to anxiety-hysteria and to depression as she is to obesity. I regard her periodic hyperphagia as a symptom of a threatened outbreak of clinical hysterical or depressive illness. I am aware that this is my interpretation of the data as cause and effect. This is so because I look at what I look through psychiatric eyes. When more precise criteria can be established, it remains to be seen whether such inferences are justified.

Group 4. *Overeating as an addiction to food.* The hyperphagia of eight patients was so classified. This is an intense kind of craving for food which is insatiable. The hyperphagia is uncontrollable and constitutes a true compulsive symptom. It often exists from early childhood. It appeared to me to be less related to external life events or to transient emotions. The analogy to alcohol and other addictions is appropriate both in terms of the behavior and the personality structure of these patients. Actually two of these eight patients had been previously addicted to alcohol, but now crave food instead of drink. Such patients may hoard or carry food. Some steal food or the money with which to buy it. One 17 year old girl had physical fights with her parents when they refused to give her money to go on eating sprees. She spontaneously compared her eating jags at drug stores, diners and restaurants with an alcoholic "making his rounds".

You have undoubtedly noted that my groupings total more than the original 18 patients. This is so because the categories are artificial, the criteria for classification as yet tentative and therefore the groups do indeed overlap. My thought in trying to delineate such groups is that within the single parameter of psychologic factors, there seem to be multiple meanings relating to hyperphagia. If we can separate out the more benign psychologic factors from the more malignant, the more transient from the more chronic, the more conscious from the less conscious, we should have a more rational basis for therapy. It may help us to understand which groups of patients should be managed by the general physician, internist or dietitian and which ones should be referred to the psychiatrist.

Because all these 18 patients were psychiatric referrals, I am currently interviewing unreferred and randomly selected patients from our Medical Clinic at the Strong Memorial Hospital. I want to study the emotional factors involved in the hyperphagia of such unselected obese patients. I wish to establish more objective criteria for the classification of different psychological groups. From more accurate classification, predictions as to success in weight reduction should be feasible. I also believe that new investigative methods other than the psychiatric interview are needed.

I have therefore devised, with Dr. Vivian Harway of our Psychology Staff, a Food and Eating Sentence Completion Test for the comparison of obese with non-obese populations. How effective such an instrument will be in diagnosis and prediction remains to be studied.

Another approach which may interest you is the study of dreams of food and eating which have been reported by my patients in formal psychoanalytic therapy. A preliminary survey indicates that non-obese patients, as well as obese ones, frequently dream of food and eating. Their associations invariably lead into non-nutritional areas: their wish for love, succorance, approval or reward, their fear of sex and other topics. A completed study of 229 such dreams[23] adds support to the hypothesis that food and eating have many other symbolic meanings than nutritional. The most frequent meaning of the food and eating dream is the need for love and emotional support and a conflict around sexual desires. The patients are initially not aware of these meanings and they become revealed only after painstaking association to the dream symbols. The use of such dreams in psychoanalysis constitutes another methodologic approach to the manifold meanings of human appetites. In this regard we should not overlook the intuitive truths revealed in our language. The primary definition of appetite in Webster's dictionary[24] does not refer to food, hunger or nutrition at all. The first definition reads: "Appetite: An inherent or habitual desire or propensity for some personal gratification, either of body or mind; a craving."

I wish to conclude with a few random remarks on weight reduction. I know the practicing physicians and nutritionists in this audience are confronted daily with the practical management of the obese patient, so despite limitations of validated data, I offer the following psychiatric suggestions:

1. It may be rewarding in "working-up" the obese patient to give

some attention to emotional factors at the same time the physician is studying his patient's basal metabolism, glucose tolerance, thyroid and hypothalamic functions. In the course of history taking, can the physician detect fluctuations in appetite and/or body weight in relation to critical life experiences? Is the patient aware of eating when not hungry or in relation to strong emotions? Is the patient aware of conscious environmental pressures with which the physician can help him? Is there evidence of emotional illness, especially hysterical syndromes or depression, or unusual cravings for which the patient could be helped to consult a psychiatrist?

2. It would seem psychologically conservative to me, not to allow any patient to lose weight rapidly by any therapeutic regimen. Many patients become irritable, anxious or depressed at lower weights and a gradual readjustment of emotional as well as metabolic forces might keep this from excess. For an elaboration of this point, I refer you to the article of Hilde Bruch on the "Psychological Aspects of Reducing."[25]

3. The relationship of the physician and the dietitian to his patient is an exceedingly potent instrument for the effecting of weight loss. Consistent interest and encouragement can be far more efficacious than impersonal passing out of diet instructions without periodic return visits.

4. Serious pressure or punitive attitudes toward obesity is contraindicated. To be sure this is well meant with a professional eye on actuarial tables.[26] At the least, such an attitude is ineffective. And if it should be effective, without concomitant resolution of underlying emotional problems, major emotional upsets can result. I suspect some of the patients addicted to food should not lose weight at all. Despite a decreased life expectancy, obesity relating to addiction to food may be a healthier adaptation than addiction to alcohol or other drugs, or to serious depression.

In summary, tonight I have suggested certain psychological hypotheses relating to the hyperphagia of obese patients. Some of the hyperphagia appears to me to be entirely for non-nutritional purposes. Some eating seems to relate to underlying emotional needs of which the patient may or may not be aware. This type of hyperphagia becomes understandable as a psychic distortion of appetite in man. This is simply another type of regulatory abnormality which can contribute to the development of the obesity syndrome. As Dr. Mayer summarized for

us last year in *Nutrition Abstracts and Reviews*,[27] it is now evident that there are multiple factors in the regulation and maintenance of body weight. Disturbances may occur at any level, of which psychic distortions in appetite are one. I suspect each obese person differs in the degree of disturbance in his genic, metabolic, hormonal, humoral, hypothalamic or cortical sphere. We will adequately understand and treat the individual obese patient only when we give thorough attention to all of these factors, including the psychologic.

REFERENCES

1. Suiter, A. Walter, Public Health, and Some of the Relative Inconsistencies of the National Government. A Plea for the Establishment of a National Health Service, *Trans. Med. Soc. St. New York, 1892*:62-83.
2. Suiter, A. Walter, The Importance and the Necessity of a National Health Service, *Sanitarian, 28*:193, 1892.
3. Bruch, H. Obesity in childhood: I. Physical growth and development of obese children, *Amer. J. Dis. Child. 58:* 457-84, 1939.
4. Bruch, H. Obesity in childhood: II. Basal metabolism and serum cholesterol of obese children, *Amer. J. Dis. Child. 58:*1001-22, 1939.
5. Bruch, H. Obesity in childhood: III. Physiologic and psychologic aspects of the food intake of obese children, *Amer. J. Dis. Child. 59:*739-81, 1940.
6. Bruch, H. Obesity in childhood: IV. Energy expenditure of obese children, *Amer. J. Dis. Child. 60:*1082-1109, 1940.
7. Bruch, H. and Touraine, G. Obesity in childhood: V. The family frame of obese children, *Psychosom. Med. 2:*141-206, 1940.
8. Bruch, H. Obesity in childhood and personality development, *Amer. J. Orthopsychiat. 11:*467-74, 1941.
9. Bruch, H. Obesity in relation to puberty, *J. Pediat. 19:*365-75, 1941.
10. Bruch, H. Psychiatric aspects of obesity in children, *Amer. J. Psychiat. 99:* 752-57, 1943.
11. Stunkard, A. J. and Wolff, H. G. Correlation of arteriovenous glucose differences, gastric hunger contractions and the experience of hunger in man (abstract), *Fed. Proc. 13:*147, 1954.
12. Stunkard, A. J., Grace, W. J. and Wolff, H. G. The night-eating syndrome, *Amer. J. Med. 19:*78-86, 1955.
13. Stunkard, A. J., Van Itallie, T. B. and Reis, B. B. The mechanism of satiety: Effect of glucagon on gastric hunger contractions in man, *Proc. Soc. exp. Biol. Med. 89:*258-61, 1955.
14. Stunkard, A. J. Untoward reactions to weight reduction among certain obese persons, *Ann. N.Y. Acad. Sci. 63:*4-5, 1955.
15. Stunkard, A. J. and Wolff, H. G. Studies on the physiology of hunger: I. The effect of intravenous administration of glucose on gastric hunger contractions in man, *J. clin. Invest. 35:*954-63, 1956.
16. Janowitz, H. D. and Grossman, M. I. Hunger and appetite: Some definitions and concepts, *J. Mt. Sinai Hosp. 16:* 231-40, 1949-50.
17. Adolph, E. F. *Physiological regulations.* Lancaster, Pa., Jacques Cattell Press, 1943.
18. Adolph, E. F. Urges to eat and drink in rats, *Amer. J. Physiol. 151:*110-25, 1947.
19. Mayer, J. Glucostatic mechanisms of regulation of food intake, *New Engl. J. Med. 249:*13-16, 1953.
20. Brobeck, J. R., Tepperman, J. and Long, C. N. H. The effect of experimental obesity upon carbohydrate metabolism, *Yale J. Biol. Med. 15:*893-904, 1942-43.

21. Engel, G. L., Reichsman, F. and Segal, H. L. A study of an infant with a gastric fistula. I. Behavior and the rate of total hydrochloric acid secretion, *Psychosom. Med. 18*:374-98, 1956.
22. Hamburger, W. W. Emotional aspects of obesity, *Med. Clin. North America 35*:483-99, March, 1951.
23. Hamburger, W. W. The occurrence and meaning of dreams of food and eating; a typical dream. Presented to the Chicago Psychoanalytic Society, October 23, 1956 (to be published).
24. *Webster's New Collegiate Dictionary.* Springfield, Mass., G. and C. Merriam Co., 1953.
25. Bruch, H. Psychological aspects of reducing, *Psychosom. Med. 14*:337-46, 1952.
26. Armstrong, D. B., Dublin, L. L., Wheatley, G. M. and Marks, H. H. Obesity and its relation to health and disease, *J. Amer. Med. Assoc. 147*:1007-14, 1951.
27. Mayer, J. The physiological basis of obesity and leanness, Parts I and II, *Nutrition Abstr. Revs. 25*:597-611; 871-83, 1955.

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The New York Academy of Medicine announces the availability of the Louis Livingston Seaman Fund for the furtherance of research in bacteriology and sanitary science. Nineteen hundred dollars is available for assignment in 1958. This Fund was made possible by the terms of the will of the late Dr. Louis Livingston Seaman, and is administered by a Committee of the Academy under the following conditions and regulations:

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TEN YEAR RESULTS OF I-131 THERAPY OF HYPERTHYROIDISM*

SIDNEY C. WERNER, BENTO COELHO†, EDITH H. QUIMBY

RADIOIODINE, I-131, eight day half-life, made in the atomic pile at Oak Ridge was released for general use by the U. S. Atomic Energy Commission, July 1946. It was employed almost immediately in the treatment of hyperthyroidism, following the lead gained from the few patients treated earlier with this agent by Soley working with Hamilton and Lawrence,[1] and the small series of patients given I-131, 12 hr. half-life isotope, by Hertz and Roberts[2] and by Chapman and Evans.[3] The present report summarizes our ten year experience with I-131 given for this purpose.

During these past ten years, the results of various groups have been presented after varying intervals of experience. Also, a serious effort has been made to define the relative roles of radioiodine, surgery, and chronic antithyroid drugs in the treatment of toxic goiter.[4] Nevertheless, as pointed out in a recent editorial,[5] there is need for the presentation of results with I-131 on a wide scale, to permit both the advantages and the drawbacks of the method to be defined and to be compared with those of the other modalities of treatment.

The present report is based on the results in a series of 525 hyperthyroid patients treated and followed by the senior author at the Presbyterian Hospital in New York between October 1946 and July 1955, and observed through June 1956. Throughout the study, the physical aspects pertaining to I-131 therapy were supervised by Dr. Quimby. At the follow-up visits, the eyes were examined routinely; the majority by Dr. Day, the rest by Drs. J. Kennedy and R. Nichols who collaborated in the initial phases of the study.

The results presented herein confirm the already established fact

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that I-131 is a highly efficacious agent for the medical treatment of hyperthyroidism. Unfortunately, however, the adverse features of the use of the method still remain a source of trouble.

Methods

All patients initially were subjected to a complete medical work-up. Only patients with well-documented hyperthyroidism were treated with radioiodine, and these were selected for therapy with this modality essentially according to principles outlined elsewhere.[4] Patients younger than 40 years of age were not treated with I-131 except when there was recurrence of toxicity following surgery or when other methods were contraindicated.

During the first two years of the study, a standard dose of 3 or 4 mc. I-131 was given to all patients.[6] Only two doses were provided to any one patient, and the second dose was not administered until four months or more after the first. In subsequent years, a dose range of I-131 was established, between 1 and 8 mc. for each of the first two doses but up to 25 mc. when a third dose or more was necessary.[7] Doses were repeated at two month intervals, provided toxicity remained severe and I-131 uptake elevated. Otherwise, the patients were observed for four months or longer according to earlier practice. According to this schedule, the smaller dose levels were employed for patients with small glands and low toxicity, the larger ones for big glands and high toxicity. Maximal doses were given only when biological resistance to radiation effect was evident from failure of the preceding doses. Withal, the average initial dose throughout the study for the great majority of patients was approximately 6 mc.

Subsequent to 1950, antithyroid drugs were given routinely in conjunction with I-131.[8, 9] As a rule, drug therapy was begun two to seven days after I-131 administration, and was continued for five to six weeks, in an effort to control toxicity during the latent period until I-131 effect becomes evident. In the past two years, thyroid by mouth has been added to the regimen. The latter drug has been given in an effort to prevent the rate and extent of reduction in level of thyroid hormone thought to provoke onset of, or exacerbation of, complicating severe infiltrative ophthalmopathy.

Changes were made in the standardization of the millicurie of I-131 several times during the ten years of the study. The present "standard"

millicurie of the Bureau of Standards is 80 per cent of the "New York" millicurie in use until January, 1955, i.e., the patients received 1.2 present "standard" mc. per tabulated mc. prior to January, 1955. All doses were given orally; the usual precautions for the safety of patient and personnel necessary for the use of these large quantities of I-131 were observed. Twenty-four hour uptake readings were made routinely for the first five years of the study but are done now only when a preliminary uptake determination with a test dose has not already been made. Effective half-life of the isotope within the gland was estimated routinely from weekly measurements over the neck but this practice was also discontinued five years ago. Calculations of the radiation dose provided to the gland were also made routinely from this value, from the dose of I-131, from estimated gland size and from the I-131 uptake. However, since the radiation dose to the thyroid was not found to correlate satisfactorily with the therapeutic result,[6] this calculation was not attempted further.

Once remission had been achieved and sustained for a year, the patients were seen annually in follow-up. At these visits, a clinical appraisal of their general and thyroid status was made. In the laboratory, B.M.R. and fasting cholesterol determinations were performed routinely; in case of doubt, the 24 hour I-131 uptake and serum precipitable iodine (SPI) level chemically were also measured. The SPI test has now replaced the former two tests as the routine. The eyes were examined by the ophthalmologist from the beginning of the study, and were measured with the Hertel exophthalmometer.

When hypothyroidism resulted from I-131 therapy, the patients were treated with thyroid for six months or more. Therapy was then discontinued in order to exclude the possibility that the hypothyroidism might have been only transient. In some instances, treatment was resumed and discontinued several times in this effort to establish the correct diagnosis.

Results of Treatment

As stated, there are 525 patients in the present series. Of these, 282 (54 per cent) had toxic diffuse goiter prior to treatment, 151 (29 per cent) toxic recurrent goiter, and 92 (17 per cent) toxic nodular goiter (Table I). The last diagnosis was made when one or more definite and discrete nodules were palpated within the gland and after every

TABLE I.—TEN YEAR EXPERIENCE WITH I-131 TREATMENT OF HYPERTHYROIDISM

Oct. 1, 1946—May 31, 1956

Sex and age distribution and type of goiter before treatment—525 patients

Type of Goiter	Sex and Age				
	Male		*Female*		
	Under 40	*40 & Over*	*Under 40*	*40 & Over*	*Total*
	(No. Patients)				
Toxic diffuse	13	65	67	137	282 (54%)
Toxic recurrent	6	17	43	85	151 (29%)
Toxic nodular	1	16	3	72	92 (17%)
Total	20	98	113	294	525 (100%)

Summary

Age	
Under 40	133
40 & over	392
Sex	
Men	118
Women	407

TABLE II.—NO. OF DOSES OF I-131 IN PATIENTS ENTERING REMISSION—447 OF 525 PATIENTS

No. of Doses	Type of Goiter			
	Diffuse	*Toxic Recurrent (No. Patients)*	*Nodular*	*Total Patients*
1	124	78	44	246 (55%)
2	74	32	24	130 (30%)
3	33	9	13	55 (12%)
4	8	1	1	10 (2%)
5	2	2	1	5 (1%)
6	1	0	0	1
Total	242	122	83	447 (100%)

TABLE III.—TOTAL DOSAGE OF I-131 IN PATIENTS ENTERING REMISSION—447 OF 525 PATIENTS

Dosage mc.	Type of Goiter *Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*	*Total Patients*
0 - 3	53	29	7	89 (20%)
4 - 6	94	60	36	190 (43%)
7 - 9	38	21	9	68 (15%)
10 - 14	42	6	11	59 (13%)
15 - 25	6	6	15	27 (6%)
Over 25	9	0	5	14 (3%)
Total	242	122	83	447 (100%)
Summary				
0 - 6	147 (61%)	89 (73%)	43 (52%)	
7 - 14	80 (33%)	27 (22%)	20 (24%)	
15 -	15 (6%)	6 (5%)	20 (24%)	
Total	242 (100%)	122 (100%)	83 (100%)	

effort had been made to differentiate nodularity from exaggerations of the normal lobulations of the gland resulting from hypertrophy.

There were 118 men and 407 women in the series with the age distribution shown in the table.

Eighty-five per cent of the patients treated were rendered euthyroid or hypothyroid by the first dose of I-131. The remaining 15 per cent required more than two doses (Tables II and VII). The majority of patients responded to less than 10 mc. total dosage, only 21 per cent requiring more than this (Tables III and VIII). The average total dosage was 6 mc., excluding the 19 highly resistant patients requiring more than 25 mc. to gain remission.

Of the 525 patients in the series, 341 were treated five years to ten years prior to the present review. One hundred fifteen of the 341 were still coming to the follow-up clinic. One patient of the series is known to have died, from metastases of a malignant melanoma noted one and one half years after I-131 therapy.

Incidence of Induced Euthyroidism: In Tables II and III are listed the number of doses, and total dosage, of I-131 required to restore

TABLE IV.—GLAND SIZE* BEFORE I-131 THERAPY AND NUMBER OF DOSES REQUIRED TO INDUCE EUTHYROIDISM—447 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*No. Doses*		
		1	*2-3*	*Over 3*
		(No. Patients)		
Toxic diffuse	Small	59	35	1
	Moderate	48	48	4
	Large	17	23	6
	Total	124	106	11
Toxic recurrent	Small	53	21	1
	Moderate	23	16	2
	Large	2	4	0
	Total	78	41	3
Toxic nodular	Small	15	6	0
	Moderate	18	15	0
	Large	11	16	2
	Total	44	37	2

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

TABLE V.—GLAND SIZE* BEFORE I-131 THERAPY AND TOTAL DOSAGE REQUIRED TO INDUCE EUTHYROIDISM—447 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*Total Dosage*			
		0-3	*4-9*	*10-25*	*Over 25*
		(No. Patients)			
Toxic diffuse	Small	34	40	12	0
	Moderate	17	59	23	1
	Large	2	23	13	0
	Total	53	122	48	1
Toxic recurrent	Small	27	45	3	0
	Moderate	2	31	8	0
	Large	0	5	1	0
	Total	29	81	12	0
Toxic nodular	Small	6	13	1	1
	Moderate	1	22	10	0
	Large	0	10	15	4
	Total	7	45	26	5

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

TABLE VI.—INCIDENCE OF PERMANENT HYPOTHYROIDISM—78 OF 525 PATIENTS

	Years after I-131 Therapy	*No. of Patients*	
	0 - 1	40	
	1 - 2	1	
	2 - 3	12	
	3 - 4	12	
	4 - 5	3	
	5 - 6	3	
	6 - 7	3	
	7 - 8	3	
	8 - 9	0	
	9 -10	1	
Summary			
	Within 1st year	40	(7.6% of 525 patients)
	After 1st year	38	(7.2% of 525 patients)
Total		78	(14.8% of 525 patients)

euthyroidism. This status was achieved in 447 of the 525 patients. One dose was sufficient in 246 (55 per cent) of the 447, whereas 16 patients (3 per cent) required more than three doses. Total dosage was less than 10 mc. in 347 patients (78 per cent) but exceeded 25 mc. in 14 (3 per cent).

Gland size prior to I-131 therapy has been correlated with number of doses of I-131, and total dosage, in Tables IV and V. It is clear that the correlations are, at best, rough.

Incidence of Induced Hypothyroidism: Transient hypothyroidism was observed in 11 patients. These patients recovered without need for sustained substitution therapy. A diagnosis of permanent hypothyroidism following I-131 therapy was made in 78, 14.8 per cent of the 525 patients in the series (Table VI). Hypothyroidism became evident within the first year after I-131 therapy in 40 patients, 7.6 per cent of the total series treated (Table VI). However, this incidence rose progressively as the patients were followed subsequent to treatment. Thus, an additional 38 patients (7.2 per cent) became permanently hypothyroid during the ten years after treatment. There was a peak between

TABLE VII.—NO. OF DOSES OF I-131 IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

	Type of Goiter		
No. of Doses	*Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*
1	29	22	4
2	5	5	3
3	3	1	1
4	0	0	1
5	2	0	0
6	0	1	0
Over 6	1	0	0
Total	40	29	9

TABLE VIII.—TOTAL DOSAGE OF I-131 IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

	Type of Goiter		
Dosage mc.	*Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*
0- 3	11	5	0
4- 6	22	17	3
7- 9	4	3	4
10-14	0	3	0
15-25	0	0	1
Over 25	3	1	1
Total	40	29	9

two and four years after therapy; one patient became hypothyroid as late as the tenth year of follow-up. Thus, a total of 14.8 per cent of all patients treated were found to be hypothyroid over the ten year follow-up period, in contrast to the incidence of 7.6 per cent in the first year after therapy.

Whereas all but two of the 40 patients with onset of hypothyroidism in the first year after I-131 therapy had had toxic diffuse or recurrent

TABLE IX.—GLAND SIZE BEFORE I-131 THERAPY AND NUMBER OF DOSES EMPLOYED IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

Type of Goiter	Estimated Gland Size	No. Doses 1	2-3 (No. Patients)	Over 3
Toxic diffuse	Small	15	5	0
	Moderate	11	2	0
	Large	3	1	2
	Total	29	8	2
Toxic recurrent	Small	13	2	0
	Moderate	7	4	0
	Large	2	0	1
	Total	22	6	1
Toxic nodular	Small	1	0	0
	Moderate	2	2	1
	Large	1	2	0
	Total	4	4	1

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

goiter before treatment was given, seven of the 38 patients developing hypothyroidism later had had toxic nodular goiter initially.

Number of Doses and Total Dosage of I-131: A single dose of I-131 was given to 55 of the 78 patients becoming hypothyroid (Table VII). Total dosage amounted to 6 mc. or less; in fact, 16 of the 55 patients became hypothyroid after 1 to 3 mc. (Table VIII). In contrast, five patients received more than three doses and five patients received more than 25 mc. before becoming hypothyroid.

Initial Gland Size: An analysis of gland size prior to treatment was made in relation to number of doses and total dosage of I-131, as was done for the patients becoming euthyroid. Tables IX and X show the distributions to be similar to that of the euthyroid group.

Effect of Pregnancy After Therapy: Eighteen patients became pregnant after remission was obtained by I-131 therapy (Table XI). Of these seven became hypothyroid, three during, and four subsequent to, the pregnancy. The offspring at birth were normal and healthy.*

* Three patients received I-131 in the first month of pregnancy when the late mensis was attributed to the hyperthyroidism or was not mentioned. The newborn also were considered healthy and normal, and remained well subsequently.

TABLE X.—GLAND SIZE* BEFORE I-131 THERAPY AND TOTAL DOSAGE EMPLOYED IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*Total Dosage in mc.*			
		0-3	*4-9*	*10-25*	*Over 25*
		(No. Patients)			
Toxic diffuse	Small	9	11	0	0
	Moderate	2	11	0	0
	Large	0	3	0	3
	Total	11	25	0	3
Toxic recurrent	Small	5	10	0	0
	Moderate	0	8	3	0
	Large	0	2	0	1
	Total	5	20	3	1
Toxic nodular	Small	0	1	0	0
	Moderate	0	4	0	0
	Large	0	2	1	0
	Total	0	7	1	0

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

Incidence of Late Recurrence: Recurrence of hyperthyroidism after one year or more of remission was observed only six times (1.1 per cent) in the series, none later than four years after treatment (Table XI). Remission was readily induced by retreatment with I-131.

Ophthalmopathy: Eye changes were classified into two clinical groups as described elsewhere.[4] The term "non-infiltrative" represents those eyes showing proptosis or widening of the fissures without other ocular manifestations, and the term "infiltrative" represents those eyes showing clinical manifestations suggestive of edematous and cellular infiltration of the ocular structures, such as chemosis, corneal ulceration, lacrimal gland swelling, or ocular muscle weakness. The purpose in classifying the eye changes is discussed later in this paper.

The course of the eye complications was described as "improved", "static", or "worse". By the last is meant progressive ocular involvement leading either to permanent impairment of the motion of the globes (usually with one or both eyes turned down and in) or of vision, or to the need for orbital decompression surgically. No patient in this series however required decompression. If there was transient and

TABLE XI.—RECURRENCE OF HYPERTHYROIDISM 1 YEAR OR MORE AFTER REMISSION—525 PATIENTS

Type of Goiter	Year of Recurrence after Therapy (No. Patients) 1	2	3	4	Over 4	Total (No. Patients)
Toxic diffuse	0	2	1	0	0	3
Toxic recurrent	0	0	1	1	0	2
Toxic nodular	0	1	0	0	0	1
Total	0	3	2	1	0	6 (1.1%)

TABLE XII.—EFFECT ON THYROID STATUS OF PREGNANCY COMMENCING AFTER REMISSION INDUCED BY I-131 THERAPY—18 OF 525 PATIENTS

Total becoming pregnant		18
Total becoming hypothyroid with pregnancy		7
During	3	
Following	4	
Initial Goiter		
Toxic diffuse		12
Toxic recurrent		6
Age range	20-39	

TABLE XIII.—INCIDENCE OF OPHTHALMOPATHY—525 PATIENTS

Type of Goiter	Total Patients	Type of Ophthalmopathy Non-infiltrative	Infiltrative	Total and % of Group
Toxic diffuse	282	49	48	97 (34%)
Toxic recurrent	151	36	19	55 (36%)
Toxic nodular	92	7	4	11 (12%)
Total	525	92	71	163 (31%)

Summary

Non-infiltrative	92 (18%)
Infiltrative	71 (13%)
Both Types	163 (31%)
Total patients in series	525 (100%)

TABLE XIV.—INCIDENCE OF OPHTHALMOPATHY AND SEX DISTRIBUTION —525 PATIENTS

Type of Goiter	*Type of Ophthalmopathy*	*Sex*		*Total*	
		Male	*Female*		
Toxic diffuse	Non-infiltrative	13	36	49	
	Infiltrative	20	28	48	
Toxic recurrent	Non-infiltrative	9	27	36	
	Infiltrative	2	17	19	
Toxic nodular	Non-infiltrative	0	7	7	
	Infiltrative	2	2	4	
	Total	46	117	163	(31%)

limited advance in chemosis or proptosis followed by return to the original status or better, the patients were not classified as "worse".

Non-infiltrative Ophthalmopathy: There were 92 patients classified as having non-infiltrative ophthalmopathy before operation (Tables XIII-XVI). Of these, 86 either improved or showed no significant change except for 1 or 2 mm. advance in proptosis. Six of the 92, however, made a transition to the infiltrative form, and one of these six ultimately developed severe and permanent muscle function impairment. Following therapy with I-131, two patients with no evident eye changes before the procedure had the onset of non-infiltrative ophthalmopathy. Neither patient in this latter group had an initial diagnosis of toxic nodular goiter. However, an initial diagnosis of toxic nodular goiter was made in seven of the 92 patients with non-infiltrative ophthalmopathy.

Infiltrative Ophthalmopathy: Prior to I-131 therapy, 71 patients were classified as having infiltrative ophthalmopathy (Tables XIII-XVI). Many of these were accepted for treatment after having been rejected by the surgeons for fear of flare-up of the eye complication. Of these, 64 either improved or showed no significant change, except possibly for 1 or 2 mm. advance in proptosis. Eight patients without previous evident eye involvement had onset of infiltrative changes subsequent to I-131 administration.

Of all in the infiltrative group, seven became "worse" and had

TABLE XV.—TYPE OF OPHTHALMOPATHY AND TIME OF ONSET—163 OF 525 PATIENTS

Type of Ophthalmopathy	Time of Onset: *Before I-131*	*After I-131: Hyper.*	*Eu.*	*Hypo.*	*Change after I-131 to Infiltrative Ophthalmopathy (No. Patients)*
		(No. Patients)			
Toxic Diffuse					
Non-infiltrative	47	1	1	0	4
Infiltrative	43	2	2	1	—
Toxic Recurrent					
Non-infiltrative	36	0	0	0	2
Infiltrative	17	1	1	0	—
Toxic Nodular					
Non-infiltrative	7	0	0	0	0
Infiltrative	3	0	1	0	—
Total	153	4	5	1	6

Summary

Patients with onset after I-131		10
Non-infiltrative	2	
Infiltrative	8	
Non-infiltrative becoming infiltrative after I-131		6
Total with onset of infiltrative ophthalmopathy after I-131		14 (2.7% of 525 patients)

permanent severe ocular muscle damage as a consequence. One of the seven also developed optic neuritis with permanent impairment of vision. This patient had, in addition to his hyperthyroidism, pernicious anemia and diabetes mellitus, although both these were reasonably well-controlled at the time of onset of the optic neuritis. Thus, with the one patient in the non-infiltrative group who developed infiltrative changes and ultimately muscle damage, there were eight patients or 1.8 per cent of the total series who became "worse" by the definition above.

The records of the patients whose ophthalmopathy commenced following I-131 therapy were reviewed to determine the status of the thyroid at the time of onset (Table XV). Of the eight patients, four were euthyroid, none hypothyroid, and three actively hyperthyroid.

An initial diagnosis of toxic nodular goiter was made in four patients of the group with infiltrative ophthalmopathy.

TABLE XVI.—CLINICAL COURSE OF OPHTHALMOPATHY—163 OF 525 PATIENTS

Non-infiltrative—92 patients		
Improved		2 (2% of non-infiltrative group)
Static		84
Change to infiltrative		6 (6% of non-infiltrative group)
Improved	3	
Static	2	
Worse with muscle fibrosis	1	
Improved or static		91 (93% of non-infiltrative group)
Infiltrative—71 patients		
Improved		6
Static		58
Improved or static		64 (90% of infiltrative group)
Worse		7 (10% of infiltrative group)
Muscle fibrosis or weakness	7	
Optic neuritis and amblyopia	1*	
Summary		
Both types of ophthalmopathy		
Improved		8 (1.8% of 525 patients)
Static		148
Worse		8 (1.8% of 525 patients)

* Also included under "muscle fibrosis"

Miscellaneous Complications: The occurrence of transient thyroiditis and of tracheitis after I-131 therapy for hyperthyroidism has been described in earlier publications.[6, 10] These complications are clinically of minor importance and their incidence has not been quantitated in this paper. Parathyroid injury[11] and leukemia[12] were not observed.* One patient in the series had chronic leukemia as well as hyperthyroidism before I-131 was given. Pericarditis with effusion occurred twice in the series, both times with onset about three weeks after therapy and with no satisfactory etiologic factor elicited.

Recurrent Nodularity: Two patients with toxic nodular goiter treated with I-131 developed readily palpable nodules in the thyroid region several years after thyroid tissue had become impalpable. The recurrent masses were removed surgically for pathologic examination.

* Since this series was reported, acute leukemia developed in one patient, 18 months after she received a total of 2.1 mc. I-131. This patient's record is being reported in detail elsewhere.

Multiple microfollicular adenomata were demonstrated in each instance. The significance of these findings is discussed later in this paper.

Localized Myxedema: This rare, cosmetically disturbing complication occurred twice in the series. Both patients had had toxic diffuse goiter, with onset of the localized myxedema prior to therapy in one, subsequently in the other. Neither patient became hypothyroid. Ophthalmopathy of the non-infiltrative type was present in both.

Thyroid Storm: Flare-up of Toxicity: One instance very suggestive of thyroid crisis or storm occurred in one of the patients in this series who developed pneumonitis about two weeks after I-131 was administered. This patient recovered. One patient treated subsequent to the analysis of the series developed "storm" 24 hours after 4 mc. I-131, with subsequent recovery.

Flare-up in toxicity occurred in six patients, especially serious in three because of exacerbation of cardiac failure. This occurred in the first two weeks after the I-131 was administered.

Hypercholesterinemia: Levels of cholesterol over 300 mg. per cent were maintained in 26 of the 447 patients rendered euthyroid by I-131 therapy. Four of these had been elevated prior to therapy; eight values had not been determined before treatment. The remaining 14 had had normal values. Ten of the 26 patients had not gained weight following remission of hyperthyroidism. Thyroid was ineffective in reducing the elevated levels except transiently.

Radiation Dosage: Calculations of radiation dosage delivered to the thyroid revealed a wide spread of values among the patients in the series. Hypothyroidism was induced by as little as 2700 rads and remission barely induced by more than 30,000 rads, although this patient later became hypothyroid.

Discussion

It is evident from past experience that all patients with hyperthyroidism can be rendered euthyroid or hypothyroid with I-131 therapy. However, it is equally clear that only a little more than half the patients in the present experience responded to a single dose. In fact, a sizable minority were still actively hyperthyroid six months and several doses after starting treatment. This unpredictability of outcome has been

observed by all workers in the field[13] and represents one of the limitations of internal radiation therapy. However, the difficulty is minimized by the use of an adjuvant antithyroid drug or iodine therapy. Thus a patient can be rendered and maintained euthyroid by these agents, except for those brief intervals when drug treatment must be discontinued to establish whether more I-131 is required, or not.

Flare-up of toxicity without fatality shortly after I-131 was administered occurred several times in our series. One death from thyroid storm has been reported in the literature seven days after 4 mc. I-131 was given.[14] The senior author also has seen a fatal outcome in a patient not included in the present series, seven days after 5 mc. I-131 given by another physician. Riggs[15] observed that the serum precipitable iodine level may increase after I-131 therapy for hyperthyroidism. However, Rall[16] states that he has been unable to find thyroglobulin in the serum following I-131 therapy of hyperthyroidism although such material is present five to ten days after the larger doses of I-131 given to patients with thyroid carcinoma or to euthyroid patients with heart disease.

It is thus likely that flare-up of toxicity or "storm" occurring within the first week after the smaller doses given in hyperthyroidism is not related to the therapy, but is an intercurrent event. Nonetheless, patients with cardiac complications, with prolonged thyrotoxicosis and severe wasting, or with big glands, probably should be given relatively small initial doses of I-131, and these should be followed shortly by an antithyroid drug or iodide administration. On occasion, it may be better to give antithyroid drugs prior to I-131 therapy, until the patient's condition is improved. I-131 can then be administered without fear of crisis.

Attention has already been called to the factor within the thyroid of biological variability in sensitivity to radiation affect.[6] The existence of this phenomenon has been amply confirmed in the present experience. Hypothyroidism resulted from as little as 2700 rads and lack of remission from over 30,000 rads, both extremes in patients with toxic diffuse goiter.

In several patients, there was an unquestionable, although limited, initial response to relatively small doses of I-131, followed subsequently by little response to considerably larger doses. It is thus suggested that the thyroid may have developed resistance to radiation effect. There is no method presently available for documenting this hypothesis. One

explanation for this phenomenon would involve differences in cell sensitivity. The radiosensitive cells in the gland would be killed with the early doses. The radio-resistant ones would remain to multiply and sustain the hyperthyroidism.

In some instances of seeming resistance to radiation effect, errors in estimation of gland size may account for the poor success from a given dose. The gland can be considerably larger than was estimated by palpation, due to rotation behind the trachea or to substernal extension. Thus failure of treatment would be due to the miscalculation in dose of I-131 administered.

McCullagh and Richards[17] have observed that patients with toxic nodular goiter are more resistant to I-131 effect than those with toxic diffuse or toxic recurrent goiter. This did not hold entirely in our series. Thus two doses and 9 mc. induced remission in most patients regardless of the initial diagnosis. McCullagh's patients were in an endemic goiter area but Chapman and Maloof in Boston[18] had an experience similar to McCullagh. One patient has been reported with toxic nodular goiter who failed to respond to 100 mc. given in a single dose.[19]

Iodine or antithyroid drugs given in conjunction with I-131 therapy have been thought to increase resistance to I-131 effect.[8] In part, the effect is only apparent since these drugs block recirculated I-131 from entering the gland and slightly shorten the effective half-life of the isotope within the gland.[20] However, these agents may induce changes in thyroid cell height and activity, or in vascularity of the gland, or both. Such changes could truly increase resistance to radiation effect.

Thyroid cancer consequent to radiation effect was not observed in the present series nor in approximately 13,000 patients of the recently pooled experience of a number of clinics.[21] It is dubious however that this can be taken to mean that such malignancies may not develop. It was originally estimated that thyroid cancer after I-131 therapy would occur, if it did so, about 20 years after therapy.[22] However no estimate was made of the range about this mean; and the range could as well be from 18 to 22 years as from 10 to 30 years. Carcinoma of the thyroid has been produced by I-131 in rats,[23] but this work has not yet been confirmed and thyroid cancers have been shown to occur spontaneously with relative frequency in the Long-Evans strain used in the original study.[24]

Persistent bizarre nuclear changes within the thyroid cells have been

described in man as late as five years after I-131 therapy.[25] Two patients of the present series developed multiple adenomata of the thyroid following I-131 therapy for toxic nodular goiter after all palpable thyroid tissue had disappeared for two and one and a half years respectively. These nodules persisted and even increased despite large doses of thyroid by mouth. The occurrence of adenomata is of interest in view of the high association rate of such lesions with thyroid cancer.[26] However, multiple adenomata are seen not infrequently in nodules which have recurred after surgery for toxic nodular goiter. Also, one of the two patients probably had chronic thyroiditis even prior to the administration of I-131, so that it is likely that this disease rather than radiation effect was responsible for the changes observed. Similar histological findings have been described in persistent nodules of toxic nodular goiter not disappearing with I-131 therapy,[27] or remaining postoperatively.

Since, despite all, the possibility remains that late cancer may yet result from treatment with I-131, it appears wise to continue the age restriction upon the use of the isotope in primary toxic goiter currently in effect in many clinics. According to this practice, patients under 40 years of age are regularly treated by other means than I-131, although there are exceptions.[4]

The presence of toxic nodular goiter is held not to contraindicate I-131 therapy in patients over 40. The spontaneous incidence of associated cancer is not much greater than in toxic diffuse goiter,[28] unlike the high rate of association in nontoxic nodular goiter.[29, 30] Thus it is believed that I-131 will not predispose to malignancy more in this group than in toxic diffuse goiter.

Recently, there has been added another objection to treatment with I-131 in younger patients with hyperthyroidism. There is a risk that incidental radiation to the gonads may increase the likelihood of mutant offspring, should these patients become parents.

Glass[31] has estimated the effect of radiation from I-131 therapy upon the mutation rate in the offspring of the population as a whole, and in the progeny of the particular patient. From a liberal estimate of the number of patients of childbearing age who might be treated annually and from the dosages in current use, he has estimated that the increase in mutations from this cause will have virtually no meaning for the population at large. To quote him:

"The average gonadal dose can be estimated to be about six rads per person from data presented at the recent Atomic Energy Commission sponsored conference on I-131 therapy.[32] This indicates an equivalence of about 1 rad to the gonads from 1 millicurie of radioiodine administered. The effect upon the population as a whole must be regarded as negligible because of the small number of individuals being treated. Thus one can assume that 100,000 persons under 40 years of age are given radioiodine in the course of a human generation, a number which is much greater than actually now given such treatment. The product would be 1500 mutations scattered in the descendants of these 100,000 persons in a population of 100 million persons per generation. Ten r, the permissible dose set by the National Academy of Science Committee, administered to the entire population would result in five million mutations. The ratio works out 0.03 per cent or 3/10,000 of what might be considered a critical limit. Even if 100,000 persons were treated per year, this would produce only 45,000 mutations, which works out at 0.9 per cent of the permissible limit. Since the administration of radioiodine is only one of many sources of radiation exposure to which the population is subject, I would think personally that this latter level would begin to be of some significance.

"If the administered dose averaged 36 rads, this would about equal the dose that would double the spontaneous mutation rate from all sources, including the background radiation."

However, the situation for the individual patient is somewhat different. As just seen from Dr. Glass' estimates, the possibility of tangible genetic defects in the progeny of the I-131 treated individual is about 1 to 2 per cent (1500 mutations per 100,000 patients at risk) with the usual doses employed in the treatment of hyperthyroidism, about 10 per cent of which would appear in the first generation. Such a likelihood may be small percentagewise. Yet, if confirmed, it would seem to be too large to warrant I-131 therapy in the younger age groups when only uncomplicated hyperthyroidism is being treated, and not cancer. Surgery in this age group is effective; is presently associated with virtually no mortality; and carries no such genetic risks or fear of carcinogenesis. Chronic antithyroid drug therapy also is available for the younger patient although the method carries a lower permanent remission rate than operation.

Obviously, these arguments against the use of I-131 in younger people are less important when the toxic goiter has recurred after a previous operation. The greater morbidity and sharply decreased efficacy of surgery when a second operation or more is required, make I-131 the method of choice.

The occurrence of acute leukemia after I-131 therapy for thyroid cancer is well-recognized and had been anticipated as a risk of the

doses of I-131 required. With these doses, whole body radiation may reach or exceed the dose level of 30-50 r which is the dose which has been estimated by some to double the spontaneous incidence rate of leukemia in the population as a whole.[21] The doses of I-131 usually employed in hyperthyroidism, however, provide radiation doses well below this doubling dose. Nonetheless, if the effect of radiation is proportional to the dose, there should be an increase in leukemia even with low dose levels, i.e., 10 per cent increase for 5 r. Withal, an occurrence of leukemia at these lower doses would be more apt to be a spontaneous event and not the consequence of the I-131 therapy.

This hypothesis seems borne out by the results presented at the recent Atomic Energy Commission sponsored conference on I-131 therapy.[32] Four patients in the 13,000 followed from one to ten years after I-131 therapy for hyperthyroidism were reported to have developed acute leukemia, i.e., four per 65,000 patient years. This incidence corresponds to the expected spontaneous incidence of acute leukemia in the general population of 1 per 20,000 patients per year, i.e., 1 per 20,000 patient years.

Our patient whose leukemia was diagnosed subsequent to the AEC conference, received a total of 2.1 mc. I-131. This represents between 1-3 rads general body exposure and a blood dose of between 2-6 rads. The whole body exposure is well below the doubling dose of 30-50 r. Where radiation effect has induced leukemia, onset has been at two years with peak incidence about six years after exposure. The present patient developed leukemia 18 months after I-131 therapy. Pochin's patient[33] included in the four above received 6.8 mc. I-131 and had onset of leukemia at 18 to 24 months after therapy. It is probable that the onset of the leukemia in both was unrelated to I-131 therapy, but it is equally clear that more data need to be collected. It becomes important that an occurrence of leukemia after I-131 therapy be reported with the details of treatment, time of onset, etc.*

The total incidence of permanent hypothyroidism after I-131 therapy is appreciable. The incidence during the first year in the present series, 7.6 per cent, is about as low as has been reported for this method, and is in the range of some surgical series.[4] However, the additional 7.6 per cent with onset during the subsequent years of follow-up makes the

* Since many patients also receive antithyroid drugs, Failla[34] has raised the question whether these latter agents may not in themselves be mutagenic and hence cause, or contribute to, the occurrence of leukemia.

total definitely greater than that of surgery. Since one patient became hypothyroid in the tenth year after therapy, the incidence may become still higher as time goes on. A possible explanation for delayed onset of hypothyroidism may lie in the abnormal pituitary-thyroid relation found to exist in active hyperthyroidism.[35] Euthyroid healthy subjects given tri-iodothyronine show a sharp decrease in I-131 uptake by the thyroid whereas overtly hyperthyroid patients show little or no decrease in uptake.[36] For the first five years following induced remission, tri-iodothyronine still does not decrease uptake in the majority of patients.[37] Subsequently, the majority of patients respond like normals. It is thus possible that the increased secretory rate of the thyroid remnant persists after I-131 therapy, and is thereby able to maintain euthyroidism but not hyperthyroidism. After five years, normal pituitary-thyroid relations may be reestablished. The hyperactivity of the thyroid remnant would end and with a decrease in secretory activity, hypothyroidism would appear.

The relative merits of radioiodine, surgery, and chronic antithyroid drugs must be even more critically scrutinized when complicating ophthalmopathy is present. It is commonly assumed that the non-infiltrative form of the disorder carries a good prognosis following surgery, and the infiltrative form a poor one. Virtually no published data are available however on which to base this assumption. It is, thus, almost impossible to compare the present results obtained with I-131 with those from surgery or antithyroid drugs. However, many of our patients with infiltrative ophthalmopathy were deliberately treated with I-131 after they were rejected by the surgeons on this account. The good results obtained suggest that I-131 may be a better form of treatment in this regard than surgery. Whether I-131 has advantages over antithyroid drugs in respect to ophthalmopathy is not known. Rapidly advancing ocular damage has been seen during antithyroid drug therapy. However, comparisons are not possible because of lack of published data.

The dearth of information about the course of ophthalmopathy after treatment of the hyperthyroidism suggests that the classification of eye changes employed in this study might be used in presenting data from other series and for other methods of therapy. This would provide comparable information so that the relative efficacies of the several methods of treatment could be appraised, or the results among clinics with any

one method evaluated. At worst, the relative incidences of patients winding up their course with severe impairment of ocular function or vision, or need for decompression, could be established.

It is recognized that the criteria employed herein for the classification of eye changes are somewhat arbitrary and that the clinical pictures may frequently not fit clearly into one or the other category. It is also recognized that the several forms of ophthalmopathy may be no more than the different manifestations of a single pathogenetic process, with a range from mild to severe.[38] Nonetheless, separation of the patients into two groups is a time-honored practice,[39,40] and the validity of such distinctions cannot be established unless the effort is made to classify these patients. However, our results would seem to suggest that the separation into two groups is probably meaningless, both prognostically and mechanistically.

Conclusions and Summary

There is no question about the high efficacy of I-131 in the treatment of hyperthyroidism. However, the method carries with it certain risks, such as that of hypothyroidism, or of failure to obtain remission with any given dose. These difficulties are explained by a factor of variability in susceptibility to radiation effect.

The disadvantage of unpredictability of outcome is not too serious since it can be largely offset by the concurrent use of antithyroid drugs. Hypothyroidism too may not be troublesome, since replacement therapy is virtually complete. However, the onset of hypothyroidism may occur years after treatment and may be quite insidious. As a consequence, the relation of the new symptoms to the antecedent I-131 therapy may go unsuspected by both physician and patient, unless the patient has been previously warned of the possibility of such a development.

Uncertainty about late thyroid cancer remains after ten years of I-131 usage. This uncertainty alone probably should continue to limit the use of the isotope in the younger age groups. In addition, however, there is another and equally important reason for restriction of treatment in younger people. The radiation effect to the gonads from I-131 therapy increases the mutation rate to between 1 per cent and 2 per cent in the offspring of the treated patient. Thus, exposure of a potential parent to this risk, however small, or of younger people in general to the possible risk of cancer, seems unjustifiable at the present stage of

information. Surgery in this group is effective and carries a low mortality and morbidity.

There is a dearth of comparable data by which to define the relative success of I-131 therapy in controlling the ophthalmopathy of patients with hyperthyroidism. The present experience suggests that I-131 probably carries less risk of serious ocular damage consequent to therapy than surgery. It is also probable that I-131 therapy is not more risky in this regard than is long-term antithyroid drug therapy, whereas I-131 is a more definitive therapeutic agent for the hyperthyroidism itself.

REFERENCES

1. Hamilton, J. G. and Lawrence, J. H. Recent clinical developments in therapeutic application of radiophosphorus and radioiodine (abstract), *J. clin. Invest. 21*:624, 1942.
2. Hertz, S. and Roberts, A. Radioactive iodine in the study of thyroid physiology; use of radioactive iodine therapy in hyperthyroidism, *J. Amer. med. Assoc. 131*:81-86, 1946.
3. Chapman, E. M. and Evans, R. D. The treatment of hyperthyroidism with radioactive iodine, *J. Amer. med. Assoc. 131*:86-91, 1946.
4. Werner, S. C., editor. *Thyroid (The): a fundamental and clinical text.* New York, Paul B. Hoeber, 1955.
5. Werner, S. C. Oak Ridge radioiodine (I-131) for hyperthyroidism—tenth anniversary (Guest editorial), *J. Amer. med. Assoc. 161*:628-29, 1956.
6. Werner, S. C., Quimby, E. H. and Schmidt, C. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (eight-day half-life), *Radiology 51*:564-78, 1948.
7. Werner, S. C. Results in the treatment of hyperthyroidism with radioiodine, I-131, *Med. Clin. N. America. 36*:623-37, 1952.
8. Hamilton, H. B. and Werner, S. C. The effects of sodium iodide, 6-propylthiouracil and 1-methyl-2-mercaptoimidazole during radioiodine therapy of hyperthyroidism, *J. clin. Endocrin. 12*: 1083-94, 1952.
9. Williams, R. H. Factors influencing the effectiveness of radioiodotherapeusis, *Amer. J. Med. 7*:718-30, 1949.
10. Werner, S. C., Quimby, E. H. and Schmidt, C. Radioactive iodine, I-131, in the treatment of hyperthyroidism, *Amer. J. Med. 7*:731-40, 1949.
11. Hamilton, J. G., Durbin, P. W. and Parrott, M. The accumulation and destructive action of Astatine-217 (ekaiodine) in the thyroid gland of rats and monkeys, *J. clin. Endocrin. Metab. 14*: 1161-78, 1954.
12. Pochin, E. E., Myant, N. B. and Corbett, B. D. Leukaemia following radioiodine treatment of hyperthyroidism, *Brit. J. Radiol. 29*:31-35, 1956.
13. Werner, S. C. The thyroid—hyperthyroidism and hypothyroidism, in *Glandular physiology and therapy*, 5. ed., Philadelphia, J. B. Lippincott, 1954, Chapt. 10, pp. 309-350.
14. Nelson, R. B., Cavenagh, J. B. and Bernstein, A. A case of fatal thyroid crisis occurring after radioactive iodine therapy, *Illinois med. J. 101*:265-68, 1952.
15. Riggs, D. S. Elevation of serum protein-bound iodine after large doses of radioactive iodine (abstract), *Fed. Proc. 7*:251, 1948.
16. Rall, J. E. Atomic Energy Commission sponsored conference on 10 years of I-131 therapy. Argonne Hospital and University of Chicago, Nov. 9, 1956. To be published.
17. McCullagh, E. P. and Richards, C. E.

Radioactive iodine in the treatment of hyperthyroidism. *A.M.A. Arch. intern. Med. 87*:4-16, 1951.

18. Chapman, E. M. and Maloof, F. Use of radioactive iodine in diagnosis and treatment of hyperthyroidism: 10 years' experience, *Medicine 34*:261-321, 1955.
19. Rynearson, E. Personal communication.
20. Goldsmith, R. E., Stanbury, J. B. and Brownell, G. L. The effect of thyrotropin on release of hormone from the human thyroid, *J. clin. Endocrin. 11:* 1079-94, 1951.
21. Court-Brown, W. M. 6th International Congress on Hematology, Boston, Mass., August 1956.
22. Dowdy, A. Carcinogenesis of radioiodine, in Werner, S. C. ed. *Thyroid (The)*. New York, Paul B. Hoeber; 1955, Chapt. 16, pp. 176-182.
23. Goldberg, R. C. and Chaikoff, I. L. Induction of thyroid cancer in the rat by radioactive iodine, *A. M. A. Arch. Path. 53*:22-28, 1952.
24. Frantz, V. K. Atomic Energy Commission sponsored conference on 10 years of I-131 therapy. Argonne Hospital and University of Chicago, Nov. 9, 1956. To be published.
25. Dobyns, B. M., Vickery, A. L., Maloof, F. and Chapman, E. M. Functional and histologic effects of therapeutic doses of radioactive iodine on the thyroid of man, *J. clin. Endocrin. 13*:548-67, 1953.
26. Sloan, L. W. and Frantz, V. K. Thyroid cancer; clinical aspects, in Werner, S. C. ed. *Thyroid (The)*. New York, Paul B. Hoeber, 1955, Chapt. 24, pp. 375-396.
27. Lindsay, S., Dailey, M. E. and Jones, M. D. Histologic effects of various types of ionizing radiation in normal and hyperplastic human thyroid glands, *J. clin. Endocrin. Metab. 14*:1179-1218, 1954.
28. Lahey, F. H. and Hare, H. F. Malignancy in adenomas of the thyroid, *J. Amer. med. Assoc. 145*:689-95, 1951.
29. Beahrs, O. H., Pemberton, J. de J. and Black, B. M. Nodular goiter and malignant lesion of the thyroid gland, *J. clin. Endocrin. 11*:1157-65, 1951.
30. Cole, W. H., Majarakis, J. D. and Slaughter, D. P. Incidence of carcinoma of the thyroid in nodular goiter, *J. clin. Endocrin. 9*:1007-11, 1949.
31. Glass, J. B. Atomic Energy Commission sponsored conference on 10 years of I-131 therapy, Argonne Hospital and University of Chicago, Nov. 9, 1956. To be published.
32. Atomic Energy Commission sponsored conference on 10 years of I-131 therapy, Argonne Hospital and University of Chicago, Nov. 8 & 9, 1956. To be published.
33. Pochin, E. E., Myant, N. B. and Corbett, B. D. Leukaemia following radioiodine treatment of hyperthyroidism, *Brit. J. Radiol. 29*:31-35, 1956.
34. Failla, G. Personal communication.
35. Werner, S. C., Spooner, M. and Hamilton, H. Further evidence that hyperthyroidism (Graves' disease) is not hyperpituitarism: Effects of triiodothyronine and sodium iodide, *J. clin. Endocrin. Metab. 15*:715-23, 1955.
36. Werner, S. C. and Spooner, M. A new and simple test for hyperthyroidism employing l-triiodothyronine and the twenty-four hour I-131 uptake method, *Bull. N. Y. Acad. Med. 31*:137-45, 1955.
37. Werner, S. C. Response to triiodothyronine as index of persistence of disease in the thyroid remnant of patients in remission from hyperthyroidism, *J. clin. Invest. 35*:57-61, 1956.
38. Means, J. H. *The thyroid and its diseases*. 2. ed. Philadelphia, Lippincott, 1948.
39. Mulvany, J. H. Exophthalmos of hyperthyroidism: a differentiation in mechanism, pathology, symptomatology and treatment of two varieties, *Amer. J. Ophthal. 27*:589; 693; 820, 1944.
40. Danis, P. and Mahaux, J. Les exophthalmies simples et oedemateuses d'origine endocrinienne, *Bull. Soc. belge Ophtal. 97*:2, 1951.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

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The Nature and Variety of Diseases of Laboratory Animals and their Significance to Medical Research

J. R. M. INNES*

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There is still a tendency amongst some experimentalists to regard animals as test tubes, with an outside skin covering a variety of peculiar internal organs of unknown quality and quantity; the state of these organs is assumed to be immaterial, as long as the animal breathes and its heart throbs, so that it can be subjected to some experiment. This is not an exaggeration. On reading scientific biological literature at large, one might deduce that all groups of animals selected for experiment were 100 per cent healthy on delivery and throughout the period of experiment. It is rare to find a paper in which an author tacitly or frankly admits to the co-existence of spontaneous disease in his animals during any chronic experiment; this might render his results of doubtful validity and make the paper unacceptable by any journal. Indeed, a lengthy experience with the experimental animal, and study of its spontaneous diseases, might cause one to question the worth of many published scientific papers.

Morbidity and mortality do not cease as by divine intervention, merely because animals are passed from stock colonies to experimentalists. It has been stated that in acute experiments, when animals are killed shortly after exposure to any procedure, the existence of spontaneous disease may be immaterial. I question this queer attitude for the results of acute LD_{50} tests will vary considerably with the state of health of laboratory animals.

The provision of healthy animals of a known standard breed, strain and clinical history, and free from disease, is a prime requisite of any medical research institution.

Diseases might be placed in arbitrary categories. The outstanding group undoubtedly includes the epizootic and enzootic varieties caused by bacteria, viruses, protozoa, worms, ectoparasites or fungi. The problems vary from species to species because of differences in susceptibility. These are the main conditions which may cause high morbidity and mortality rates.

In a second group are the lesions, or disease complexes, which may be chronic and clinically silent for a long time, e.g., chronic murine pneumonia and many parasitic diseases, and which usually can be diagnosed only at necropsy.

Let us clearly recognize the difficulties in accurate and quick diagnosis of disease in small laboratory animals, and that "clinical" diagnosis in the living state is of the most superficial kind. Even naked eye examination of organs at necropsy may not be sufficient, and the smaller the animals, the more apparent are these limitations.

* Now at Wellcome Research Laboratories, Tuckahoe, New York.

To anyone with experience in the examination of laboratory animals for pathologic changes, there is known yet a host of what might be called "incidental lesions". Some of these may not interfere with general health, some may be fortuitous freaks and accidents, but they will be regularly observed if a careful search is made.

Some of the epizootic and enzootic disease can be controlled by various means, and most pathologists, over the years, become familiar with their general picture. For those involved in experimental studies, particularly implicating chronic toxicity and chronic infections, the clinically silent and incidental lesions with high morbidity rates are important. Without adequate experience, the effect of an experimental procedure on organs and tissue can be confused with lesions caused by nature. In rats derived from a colony in which there is a high morbidity rate of chronic pneumonia, a diagnosis of chronic bronchitis following exposure to toxic inhalants is almost an impossibility, but this has been recorded many times.

Inherited diseases must never be ignored (as can be seen below and by a glance at Hans Grüneberg's fascinating book on "Animal Genetics and Medicine".[3]) By ignorance of, or failure to recognize, inherited conditions, some of which may be inapparent until long after birth, sublethal and lethal factors have become widespread. Inherited diseases should be recorded and the animal strains be kept, as they are available tools of study for workers in genetics and heredo-pathology.

The possibility of spontaneous nutritional deficiencies occurring, even in these modern days, cannot be cursorily dismissed, and we still know little regarding the role of nutrition in resistance to diseases.

Finally, let us not forget that a knowledge of diseases of laboratory animals is of fundamental importance to the experimentalist who is engaged in the elucidation of diseases of man and domesticated animals, and that there are many diseases transmissible from animals to man.

A *short* listing of certain categories of diseases is appended:

A. Some Common Diseases:

RATS: Chronic murine pneumonia; infectious catarrh; middle ear disease; paratyphoid infections; leptospirosis; toxoplasmosis; meningoencephalitis caused by encephalitzoon; bartonellosis; spontaneous demyelinating disease in adult rats; myocarditis.

MICE: Salmonellosis; pasteurellosis; ectromelia; streptococcal polyarthritis; lymphocytic choriomeningitis; murine demyelinating disease; mouse viral hepatitis; grey lung virus disease; diarrheal disease of suckling mice; sarcosporidiosis; myocarditis and pulmonary phlebitis caused by rickettsia-like bodies.

GUINEA PIGS: Salmonellosis; pneumonias; pseudotuberculosis; cervical lymphadenitis; coccidiosis; salivary gland virus; "infectious paralysis"; toxoplasmosis; encephalitis; scurvy.

RABBITS: Coccidiosis (hepatic and intestinal); mucoid enteritis; snuffles; pseudotuberculosis; necrobacillosis; rabbit syphilis; pyogenic infections; ringworm; ear mange; intestinal parasites; muscular dystrophy; listerellosis; hemorrhagic typhilitis; myxomatosis; rabbit pox; posterior paralysis.

B. Inherited Conditions. A few examples selected at random include: encephalocele and spina bifida in mice and rabbits; syringomyelia in rabbits; otocephaly and other monstrosities of the head of guinea pig, mouse and rabbit; hydrocephalus in mouse and rat; eye anomalies; brachydactylism in the rabbit; ataxias and tremors; various epilepsies and audiogenic seizures in rabbits; shaking, jerking and waltzing mice; dwarfism in rabbits and mice; achondroplasia, osteopetrosis and splayleg in rabbits; latent diabetes in rats; acholuric jaundice in rats; short, fused and kinky tail of mice; short ear in mice; polydactylism in guinea pigs; hare lip and cleft palate in mice; tooth anomalies; anomalies of urogenital tract; varieties of hairlessness in mice and rabbits.

C. A few of the clinically silent and incidental lesions include calcification of the adrenal glands of monkeys and cats; aspirated fragments of bone in the lungs of rodents; calcification of the pulmonary artery

and aorta of rats; myocarditis in rats and rabbits; pulmonary adenomatosis in rats and guinea pigs; testicular atrophy and calcification in rats; ovarian abscess in rats; chronic nephritis in guinea pigs, hamsters and rabbits; giant-cell granuloma in rat lungs; corpora calcificantes in ovaries of monkeys; myodegeneration in skeletal muscle of rabbits; pancreatitis in mice; lipid metamorphosis in liver and kidneys of guinea pigs; granuloma and vascular lesions in the lungs of mice caused by fragments of hair or epidermal scales carried in by intravenous injections.

The lecture was illustrated profusely by a series of lantern slides showing macroscopic and microscopic changes in the various conditions, most of which have been themes of various papers published by the staff of the author's department.

REFERENCE

1. Grüneberg, H. *Animal genetics and medicine.* London. Hamish Hamilton, 1947.

DISCUSSION

ALFRED ANGRIST: I was surprised to hear that salmonellosis never affected rats. I thought that S. typhi murium was common in this species and other forms of salmonellosis, too. I know we produced morphologic lesions with several Salmonella strains by mouth, though we did use large doses.

J. R. M. INNES: I said *we* could not produce demonstrable experimental disease in rats, but there are remarkably few papers on salmonellosis in rats. Using the same strain of Salmonella that killed mice and hamsters we were unable to kill rats. Mr. Cummings also stated that Salmonella was an infection supposed to occur in rats, but he had not seen any acute outbreaks.

ANN POLLAK: Is it possible to get hamsters that don't have tapeworms? All of mine do, and I was wondering whether this was just in my laboratory.

J. R. M. INNES: I do not know.

HENRY SIEGEL: I should like to ask whether Dr. Innes has any ideas concerning the cause of the perifollicular hyperplasia observed in the spleens of some groups of rats, and not in other groups.

J. R. M. INNES: We have seen very little of that. Most of the rats we have examined are killed, and do not die natural deaths, but we have seen a number which we think had leukemia.

MAX WACHSTEIN: May I ask whether Dr. Innes has also noticed the diffuse granulomatous lesions in the liver, which are very bothersome in experiments with rats, particularly in those on various deficiency diets?

J. R. M. INNES: We have seen the lesion commonly in rabbits, but not in rats.

SIGMUND L. WILENS: I would like to get a little better impression as to the source of the animals, and what had been done to the animals. Are these animals on which experiments have been performed, and if so, do you feel that any experimental procedure can start up and bring to life some spontaneous disease process which ordinarily might not be present at all, or would take a long time to develop? How much part does the age of the animal play in the occurrence of these diseases, because it has been my impression with animals, as with man, that when you autopsy a young individual you find a few incidental lesions, and when you autopsy an older individual you find many.

J. R. M. INNES: There are many experimental procedures which will provoke latent or clinically silent infections, particularly in mice. Salmonellosis is an example. The source of our animals is tremendously mixed; some come from our animal colony, and some of the lesions shown have been picked up during chronic toxicity work. All the lesions of chronic pneumonia represent part of a study carried out mostly on rats from our colony, some killed for the special purpose. Our number has been built up constantly by cutting sections of lungs, and making cultures, of hundreds of rats of all ages from other sources. I think the age of the animal certainly does play a big role. We do not see

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anything like the variety of these incidental lesions in young animals as in old animals. Some of the lesions are fortuitous and may not affect the health of the animals, but they still are important. I think the finding of hair is extremely interesting, because on occasion not hair, but cotton wool fibers, have been seen in human lungs. Having seen these changes once, we have noticed them frequently in animals that have been injected intravenously repeatedly. If we had not been lucky enough to observe the hair fragments, we might have reported the toxic drug as causing peculiar granulomatous and vascular lesions in lungs.

SIGMUND L. WILENS: I take it you never have seen Hodgkin's disease in any animal.

J. R. M. INNES: I do not think any authentic instance of Hodgkin's disease has ever been reported in any animal. I have seen sarcomatous tumors in dogs' spleens, but to my knowledge there has been no report of Hodgkin's disease in its entirety in any animal, taking all the clinical and pathologic pictures into account. I think you will find that most reports of Hodgkin's disease in animals fail on that score. Usually they have been reported on the basis of the presence of one or two Dorothy Reed-Sternberg cells in a tumor of lymph node or spleen.

SIGMUND L. WILENS: Have you ever seen mitral stenosis in animals?

J. R. M. INNES: Not so commonly as in man. The mitral lesions in animals are mostly residual from some previous infection, occasionally in dogs with or after streptococcal infections.

SIGMUND L. WILENS: Have you ever seen a gallstone in an animal?

J. R. M. INNES: No, I have not.

HENRY SIEGEL: I have had a little experience along that line which I have not been able to duplicate. About 15 years ago we had a group of dogs on a pantothenic acid deficient synthetic diet. As they were brought out of their deficiency with pantothenic acid, there developed a hemolytic anemia associated with pigment calculi. The experiment was terminated because of the war. We were subsequently unsuccessful in attempts to reproduce these findings. Apparently it is something related to the diet.

ANN POLLAK: I would like to ask a little more about amyloid; was that in hamsters?

J. R. M. INNES: Yes, but I have seen little of this lesion myself.

SIGMUND L. WILENS: I have been under the impression we might find amyloid in any animal that has a chronic infection, except the rat. Have you ever seen amyloidosis in the rat? Do you think that statement is true?

J. R. M. INNES: We have not seen amyloid degeneration in rat tissues, but we see few rats over one year old.

Mouse Hepatitis in Relation to Leukemia

JOHN B. NELSON, Ph.D.

Rockefeller Institute for Medical Research, New York

The fundamental knowledge gained from studies on the native diseases of laboratory animals has contributed in no small measure to the growth of pathology. Quite apart from any theoretical value, however, this knowledge is of immediate practical significance. The accelerated pace of recent years in medical and biological research has brought about a huge increase in the use of experimental animals. Numerically the mouse is far in the lead. The United States alone produces in excess of ten million mice annually for scientific purposes. Laboratory mice are unusually susceptible animals and are subject to a wide variety of diseases. The risk of transmission is enhanced by the mass production methods necessary to rear them in quantity. For the correct interpretation of experimental findings it is essential that both the breeders and the users of mice be familiar with their disease pattern.

The present liver disease is illustrative of what may unexpectedly appear in the mouse. It was first observed during the passage of murine lymphocytic leukemia. The incidence of leukemia (lymphoma) in the random-bred Princeton mouse, maintained at the Rockefeller Institute since 1922, is close to five per cent in year-old animals. The favorite sites of development in these mice are the regional lymph nodes and the spleen. It is transferable to weanlings of the same strain by the intraperitoneal injection of organ suspensions containing the tumor cells. On passage the activity of the cells is accelerated and lesions appear by the tenth day or earlier. In addition to the usual sites, the ovarian capsule and periovarian tissues are often involved. This reaction was of particular interest because pleuropneumonia-like organisms (PPLO), which have long been studied in this laboratory, selectively localize in the ovary and oviducts on intraperitoneal injection.[1] An experiment was begun to determine the behavior of a suspension containing both PPLO and leukemic lymphocytes. Unexpected difficulties were encountered in maintaining a passage series to provide a constant supply of the tumor cells. In two series the leukemic cells failed to develop after 30-odd passages. With the third episode in which the failure occurred after 12 passages, an explanation was sought.

Two mice in the critical passage of the third series died on the ninth day and showed focal involvement of the liver at autopsy. Serial abdominal passage was then begun with a pooled liver suspension from these mice. It was soon apparent that the original leukemic syndrome had been replaced by an acute and transmissible necrosis of the liver.[2] This condition, now designated mouse hepatitis, was readily reproducible in Princeton weanlings (10 to 12 grams) by intraperitoneal injection of 10 per cent liver suspensions from dead or sickly mice. The course of the disease was brief. In one series of 100 mice 68 were dead by the fourth day. The mortality rate was practically 100 per cent.

At autopsy the only constant pathologic finding was in the liver. The characteristic histologic feature was necrosis of the hepatic parenchyma, varying in distribution from focal to diffuse. This reaction is described in some detail. Recovery from the disease was rare and generally limited to mice injected with suspensions of reduced activity. Some of these mice showed typically cirrhotic livers when killed. In no instance, however, was there any indication of leukemia. If liver suspensions were introduced by other routes, namely subcutaneous, intracerebral, intranasal, and oral, the causal agent was carried to the liver

and produced the usual lesions. It was not transmissible by direct contact unless cannibalism occurred.

The causal agent was identified as a virus.[3] On titration, freshly prepared liver suspensions showed declining activity through dilution 10^{-7}. The virus was demonstrable in the liver, spleen, kidney, heart's blood, urine, and intestinal contents of experimentally infected mice. Its activity was reduced in young adults 8 to 15 weeks old. The respective mortality and morbidity rates were 55 and 88 per cent, in comparison with 99 and 100 per cent in three to four weeks old weanlings. Infant Swiss mice were fully susceptible through the tenth day after birth, but weanlings were largely resistant. Continued passage at short intervals resulted in a modified form that was fully active.[4]

While the above work was in progress another type of mouse hepatitis was reported in England by Gledhill and Andrewes.[5] It was originally obtained from mice of the Parks strain which were relatively resistant. Weanlings of Webster's BSVS strain were highly susceptible. The intraperitoneal injection of organ suspensions and filtrates resulted in a disease syndrome essentially the same as the hepatitis of Princeton mice. Gledhill, Dick and Andrewes[6] then noted that the causal agent could be resolved into a stable component S and a labile one L. The latter was inactivated by Terramycin but not penicillin. Both components were filterable and noncultivable. Together with Niven, these authors[7] later identified the S component as a virus of low virulence and the L form as *Eperythrozoon coccoides*. The two agents were largely inactive when injected alone, but in combination regularly produced fatal hepatitis. Prior to death there was a marked increase in the number of eperythrozoa in the blood.

E. coccoides is not carried by the Rockefeller Institute strains of Princeton and Swiss mice. It was obtained, however, from an outside source and maintained by passage in unsplenectomized Princeton weanlings. It has no effect on the highly active local virus in these mice. Dual injection in Swiss weanlings was attended by lethal hepatitis and accompanied by an increased growth of the organisms,[8] substantiating the findings of the British workers.

Additional types of hepatitis virus have been isolated from the same and other strains of mice.[9-11] Some of them produce pathologic changes in the brain, on intraperitoneal or intracerebral injection, in addition to involvement of the liver. It is now apparent that there exists a family of closely related murine viruses with hepatotropic and neurotropic properties.[10] They are widely distributed in nature and apparently enzootic in both random and inbred mouse colonies. Under normal conditions these viruses are inapparent but their emergence may be brought about by the growth of leukemic cells, by *E. coccoides* and by treatment with urethane[11] or methylformamide. It is necessary to assume that they exist in a latent or immature state in an occasional mouse. Whatever their ancestral history may be they are very real entities, once they appear, and constitute an additional hazard in the use of mice for experimental purposes.

REFERENCES

1. Nelson, J. B. The selective localization of murine pleuropneumonia-like organisms in the female genital tract on intraperitoneal injection in mice, *J. exp. Med. 100:* 311-20, 1954.
2. Nelson, J. B. Acute hepatitis associated with mouse leukemia. I. Pathological features and transmission of the disease, *J. exp. Med. 96:* 293-302, 1952.
3. Nelson, J. B. II. Etiology and host range of the causal agent in mice, *J. exp. Med. 96:* 303-12, 1952.
4. Nelson, J. B. III. The natural resistance of Swiss mice to hepatitis. *J. exp. Med. 98:* 433-40, 1953.
5. Gledhill, A. W. and Andrewes, C. H. A hepatitis virus of mice, *Brit. J. exp. Path. 32:* 559-68, 1951.
6. Gledhill, A. W., Dick, G. W. A. and Andrewes. C. H. Production of hepatitis in mice by the combined action of two filterable agents, *Lancet, 2:* 509-11, 1952.
7. Niven, J. S. F., Gledhill, A. W. Dick, G. W. A. and Andrewes, C. H. Further light on mouse hepatitis, *Lancet, 2:* 1061, 1952.
8. Nelson, J. B. Acute hepatitis associated with mouse leukemia. IV. The relationship of *Eperythrozoon coccoides* to the hepatitis virus of Princeton mice, *J. exp. Med. 98:*441-50, 1953.
9. Gledhill, A. W., Dick, G. W. A., and Niven, J. S. F. Studies on mouse hepatitis virus (MHV), *6th Internat. Congr. Microbiology, Rome, 2:* 46-47, 1953.
10. Nelson, J. B. Acute hepatitis associated with mouse leukemia. V. The neurotropic properties of the causal virus, *J. exp. Med. 102:* 581-94, 1955.
11. Braunsteiner, H. and Friend, C. Viral hepatitis associated with transplantable mouse leukemia. I. Acute hepatic manifestations follow-

ing treatment with urethane and methylformamide, *J. exp. Med. 100:* 665-74, 1954.

12. Morris, J. A. and Aulisio, C. G. A new member of the hepato-encephalitis group of murine viruses (abstract), *Fed. Proc. 13:* 506, 1954.

DISCUSSION

BASIL MOUMGIS: I did not quite get the time sequence. When you said you no longer had leukemia, was it because the animals died first of the infection, and leukemia did not have time to develop?

J. B. NELSON: In passaging the highly virulent strain of Princeton hepatitis virus with a 10 per cent liver suspension that was more or less true, the time interval was too short. Using diluted suspensions, the virus developed more slowly but with no indication of leukemia.

CECIL TREIP: Did the mice which recovered and developed cirrhosis develop leukemia later on?

J. B. NELSON: I have never seen leukemia in these mice. I cannot completely answer the question because in carrying many mice it is not practical to hold individual ones for a long time. So I am not able to say that the occasional recovered mouse never develops leukemia.

SIGMUND L. WILENS: I should like to ask first whether the animals that recover from it are resistant to subsequent inoculation of hepatitis virus, whether you can transmit leukemia to them after they recover, and finally, is there any possible relationship between this virus hepatitis and the viruses that cause hepatitis in man?

J. B. NELSON: Mice that recover from the highly virulent form of Princeton hepatitis are not resistant. Actually I have had very few recovered cases to test and I am unable to answer your question about superimposing leukemia on recovery. It is something I plan to study with the less virulent strains of the virus. You also brought up the question of the relationship of mouse hepatitis to that in man. I do not see how they can be related except in the general type of reaction. Human hepatitis virus injected together with the eperythrozoon was completely inactive in mice.

SIGMUND L. WILENS: In some of your inocula you used liver tissue. Is that always done?

J. B. NELSON: I regularly use liver tissue in passaging, but spleen and blood are about equally active.

SIGMUND L. WILENS: Is there a possibility that this might lead to homologous antibody formation and play a role in making the animals susceptible to the virus?

J. B. NELSON: There is no indication of it.

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(Please Note: For the coming academic year these meetings will be held on the SECOND TUESDAY *of the month, November 1957 through April 1958, at 4:30 p.m., in Room 20 at the Academy.)*

TUESDAY
November 12
1957

MANAGEMENT OF PATIENTS WITH ANGINA

Moderator: Charles E. Kossmann

Members: Clarence E. de la Chapelle
Charles K. Friedberg
Samuel A. Thompson

TUESDAY
December 10
1957

MANAGEMENT OF SURGICAL CONDITIONS OF THE ALIMENTARY TRACT IN INFANCY

Moderator: George H. Humphreys II

TUESDAY
January 14
1958

RECENT ADVANCES IN THE TREATMENT OF THE SPRUE SYNDROME

Moderator: Thomas P. Almy

TUESDAY
February 11
1958

COMMON UROLOGICAL PROBLEMS IN GENERAL PRACTICE

Moderator: Victor F. Marshall

TUESDAY
March 11
1958

MANAGEMENT OF HEMORRHAGIC STATES

Moderator: Louis R. Wasserman

TUESDAY
April 8
1958

EVALUATION AND MANAGEMENT OF FATIGUE

Moderator: To be announced

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Wednesday
November 13, 1957
8:30 p.m.

The Linsly R. Williams Memorial Lecture

THE STRESS OF LIFE

HANS SELYE

Professor and Director, Institut de Médecine et Chirurgie Expérimentale, Université de Montreal

Wednesday
November 27, 1957
8:30 p.m.

THE FUTURE IN CANCER

JOHN R. HELLER

Director, National Cancer Institute, National Institutes of Health, U. S. Public Health Service

Wednesday
December 11, 1957
8:30 p.m.

THE FUTURE IN NUTRITION

JAMES M. HUNDLEY

Food and Agriculture Organization of the United Nations

Wednesday
January 8, 1958
8:30 p.m.

THE FUTURE IN HEART DISEASE

CLARENCE E. DE LA CHAPELLE

Visiting Physician, Bellevue Hospital; Director of Medicine, Lenox Hill Hospital

Wednesday
January 22, 1958
8:30 p.m.

FRONTIERS IN VIRUS RESEARCH

MAX A. LAUFFER, Ph.D.

Dean, Division of Natural Sciences and Professor of Biophysics, University of Pittsburgh

Wednesday
February 5, 1958
8:30 p.m.

The George R. Siedenburg Memorial Lecture

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EDITH H. QUIMBY, Sc.D.

Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University

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The programme of the French Medicine Series includes the following addresses:

THE IMPORTANT PROBLEMS RAISED BY THE ORGANIZATION OF PUBLIC HEALTH IN FRANCE—Dr. Eugene Aujaleu, Director General of the Ministry of Public Health.

MEDICAL INSTRUCTION IN FRANCE—Prof. Robert Debré, Professor of Clinical Pediatrics, Member of the Academy of Medicine.

MEDICAL RESEARCH IN FRANCE—Prof. Louis Bugnard, Director of the National Institute of Hygiene.

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ANTIHISTAMINES—Dr. Bernard Halpern, Chief of Service at the Broussais Hospital.

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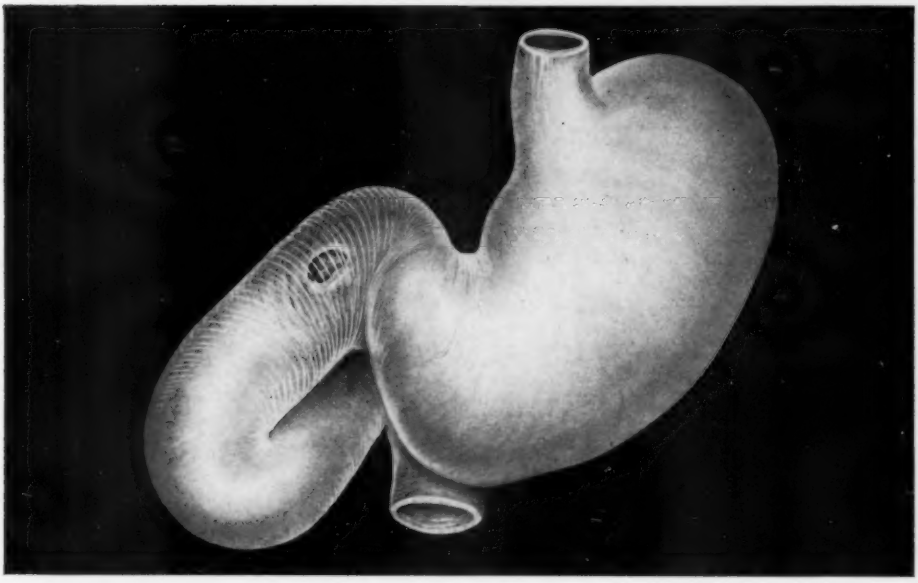

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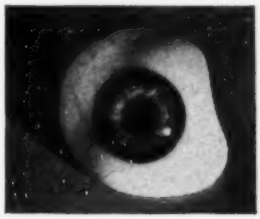

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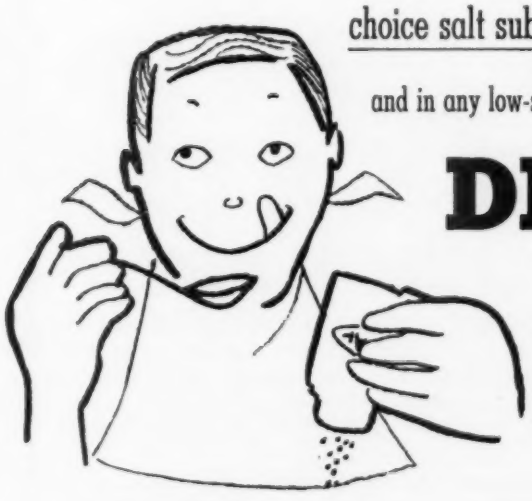

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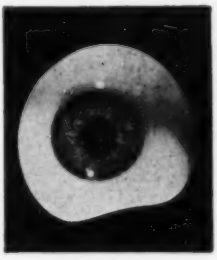

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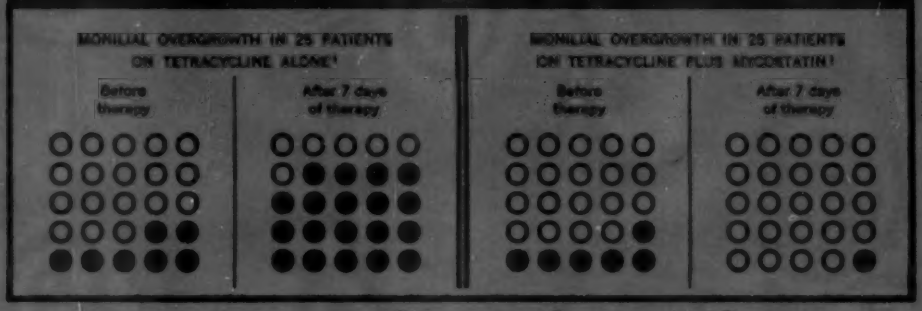

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